U.S. High Production Volume (HPV)
Chemical Challenge Program

CATEGORY DEVELOPMENT, JUSTIFICATION, AND PROPOSED TEST PLAN FOR COBALT SALTS OF C2 AND C3 CARBOXYLATES

Prepared by

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on behalf of

OM Group and The Shepherd Chemical Company

Sponsoring Members of the

The Metal Carboxylates Coalition

A SOCMA Affiliated Consortium

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SUMMARY

The cobalt salts of C2 and C3 carboxylates category includes two metal carboxylate salts cobalt acetate and co propionate that are made up of one of two simple carboxylic acids (acetate or propionate) paired with divalent cobaltions. These compounds readily dissociate to the corresponding metal cation and carboxylic acid. At a gastric pH (~1.2), the two metal carboxylates in this category are essentially completely dissociated (>99.9%) and subsequent absorption of the metal cation (e.g., Co(II)) occurs independently of the carboxylic acid. . Comparison of acute toxicity data for a series of cobalt compounds (including Co acetate) shows that when toxicity data is expressed in terms of the Co(II) ion, the toxicity of Co acetate (and other Co salts) and $Co(II)Cl_2$ are essentially equivalent.

HPV endpoints for this category are fulfilled using a combination of data, including data for the parent molecule and those for the dissociation products; that is, a soluble metal salt (e.g., Co Cl_2)) and/or a carboxylic acid. Selected testing of the parent metal carboxylates has been proposed to support the category and fill key HPV endpoints where data are not available and cannot be easily estimated. Robust summaries are provided for the parent molecules and, where available, supporting data for the carboxylic acid dissociation products are included within the "remarks" section of the Robust Summaries. Existing data for cobalt is provided as a set of robust summaries. The proposed testing is presented in the attached Test Plan matrix (Table I) and discussed below.

METAL SALTS OF C2 AND C3 CARBOXYLATES CATEGORY

The category includes the two carboxylates listed below. The Category is sponsored by the Metal Carboxylates Coalition (The Coalition) a consortium managed by Synthetic Organic Chemical Manufacturers Association's (SOCMA) Association Management Center. The Coalition is pleased to submit a Category development and justification, Test Plan and Robust Summaries for the following compounds sponsored under the U.S. High Production Volume (HPV) Challenge Program:

Chemical name	CAS#
Cobalt (II) Acetate	71-48-7
Propionic Acid, Cobalt (II) Salt	1560-69-6

USE PATTERNS FOR METAL CARBOXYLATES

The metal carboxylates function to deliver a metal ion into chemical reactions. The carboxylic acids (acids) are tailored for use in different products or chemical reactions.

CATEGORY RATIONALE

Common Characteristics of Co Acetate and Co Propionate

These two metal carboxylate salts are functionally similar and have the same general ionizable substituents, a divalent metal cation (Co), and a carboxylic acid group acetate or propionate. The general formula for the group (salt, ion pair) is as follows:

$$[RCOO^{-}]_2:[M^{+2}]$$

The carboxylic acids in this category have either a C2 (acetate) or a C3 (propionate) alkyl chain length (as shown in Fig. 1, below). These carboxylates are associated as ion pairs with cobalt. The purpose of these metal carboxylates is to readily dissociate into the free metal and free acid. Dissociation constants have been measured for the two metal carboxylate compounds in this category. Dissociation data is presented in Table 1, below. Because of the importance of the effect of ready dissociation in the characterization of the toxicity of these compounds, this physicochemical characteristic is discussed at length below.

Dissociation Studies

These chemicals are used to deliver metal catalysts to chemical processes. One key characteristic of the compounds in the Metal Salts of C2 and C3 Carboxylates Category is that they readily dissociate from an ion pair into free metal and free acid as the pH is decreased. The dissociation process is shown in equation #1. Dissociation is a reversible reaction, splitting the parent compound into two or more chemical species, which may be ionic, but are not necessarily so. Dissociation studies have been conducted for both compounds in the category following OECD Guideline 112. When compared with existing data for acetate and propionate (Table 1), the pKa values from the scientific literature are very consistent with the measured pK2 values from the dissociation studies (see numbers in bold, Table 1). The latter represent the respective equilibrium between the ionized and unionized forms of the dissociated carboxylic acids and are essentially the same for both carboxylates.. At a pH below the pK2 value, the acid moiety is in the unionized form (Equation #1).

Dissociation is a reversible process and the portion of dissociated salt present is dependent on the ambient pH and pK (the dissociation constant, pKa or pKb) of the compound, which is the pH at which 50% dissociation occurs (i.e., 50% is

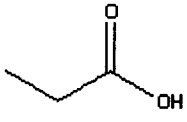
present as an ion pair). The proportion of dissociation at a particular pH may be determined from the Henderson-Hasselbalch equation (Equation #2). If the pH is lowered below the pK, the proportion of chemical in the dissociated form increases. At a pH of one unit below the pK, approximately 90% of the chemical is in the dissociated form. At two pH units below the pK, approximately 99% is dissociated, and so on. Based on data from the dissociation studies, in the low pH environment of the digestive tract (pH ~1.2), essentially complete dissociation (>99.999%) will occur for both metal carboxylates (Table 2)

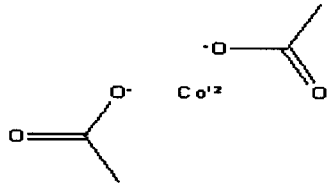
Table 1 Comparison of pK values for metal carboxylate salts and respective carboxylic acids[a]

Chemical Tested	Equilibrium Constants	
	pK1	pK2
Acetate	**4.76**	
Cobalt acetate	7.75	**4.91**
Propionate	**4.87**	
Cobalt propionate	7.58	**4.85**

[a] See Table I and the Robust Summaries for additional details.

Figure 1: Structures of Carboxylic Acids and a Carboxylate Salt Representative of C2 and C3 Metal Carboxylates





a) Propionate (as the free acid) b) Cobalt acetate- (as the salt)

Equation #1

$$[RCOO^-]_2{:}[M^{+2}] \xleftrightarrow{pK1} [RCOO^-]_2 + [M^{+2}] \xleftrightarrow{pK2} [RCOOH]_2 + [M^{+2}]$$

undissociated salt (High pH) **dissociated acid and metal** **neutral species** + ionized metal (Low pH)

Equation #2

pK1 = pH + log [(dissociated form)/(undissociated form or ion pair)]

Based on the pK1 results presented in Table 1, the influence of pH on dissociation has been calculated using the Henderson-Hasselbalch equation. Results of these calculations are shown in Table 2. The analyses indicate that

Table 2. The affect of pH on dissociation of category chemicals.

pH	Ratio of Dissociated Form to Undissociated Form (Ion Pair)(Percent in Dissociated Form)	
	Cobalt Acetate (pK = 7.75)	Cobalt Propionate (pK = 7.58)
1	5,623,413 / 1 (99.99998%)	3,801,894 / 1 (99.99997%)
2	562,341 / 1 (99.9998%)	380,189 / 1 (99.9997%)
3	56,234 / 1 (99.998%)	38,019 / 1 (99.997%)
4	5,623 / 1 (99.98%)	3,802 (99.97%)
5	562 / 1 (99.8%)	380 / 1 (99.73%)
6	56.2 / 1 (98.25%)	38.0 / 1 (97.4%)
7	5.62 / 1 (84.89%)	3.80 / 1 (79.17%)
8	0.56 /1 (35.89%)	0.38 / 1 (27.54%)
9	0.056 / 1 (5.30%)	0.038 / 1 (3.66%)

slight to moderate dissociation will occur at approximately neutral pH (i.e., representative of aquatic and marine ecosystems), while essentially complete dissociation will occur at physiologically relevant pH of the mammalian stomach (pH 1.2). These findings are particularly important in relating available data for the respective carboxylic acids and metals to support the existing data for the metal carboxylate salts in this category.

Because the free acid and corresponding free metal have much different characteristics (e.g., solubility, adsorption, and toxicity) than the undissociated salt (ion pair), the proportion of dissociation influences the behavior of the substance in the environment and *in vivo*. The bioavailable fraction of the acid and metal constituents of metal carboxylate salts can be estimated from the dissociation constants.

There are two principal hazard assessments being evaluated based on the current data for these two metal carboxylates. The first is the hazard to aquatic organisms due to environmental exposure. The second is hazard to mammalian systems as a result of oral exposure. The dissociation constants reported in Table 1 indicate that the two compounds in this category have pK (pK1) values in the neutral range. The data in Table 2 indicate that in the ambient aquatic environment, moderate portions of the metal carboxylates will be dissociated; therefore, part of the compounds will be present as metal cations (ionized). In the environment (i.e., aquatic systems), toxicity is typically related to the free metal ion concentration (EPA 2002).The metal ion pair (salt) is less likely to be absorbed and to contribute to toxicity

At the low pH of the mammalian stomach (pH 1.2) all of the metal carboxylates are expected to be completely, or nearly completely, dissociated. This indicates that when administered orally, the absorption and resulting toxicity of the metal carboxylates would be due to the independent action of the respective acid and free (ionized) metal. This is supported by *in vivo* and *in vitro* data with cobalt acetate and other cobalt containing carboxylates (Firriolo 1992.; Speijers et al 1985; Stopford et al. 2003, unpublished)(See discussion below).

The dissociation constants show that at the pH of the stomach the important moieties from a toxicological standpoint are the unionized free acid and ionized metal. Because of this dissiociation in the stomach, mammalian toxicity data for the free acid, or that for a simple salt of the acid (e.g., the sodium salt or the calcium salt), can to serve as a surrogate data for the acid component of the two metal carboxylates in this category. Table 3 shows how similar the acute toxicity data is for the two acids in this category, acetate and propionate.. Similarly, under these conditions, data for the metal ion can be represented by fate and toxicity data for free metal ion or simple metal salts (e.g., metal chlorides). Therefore, the role in any observed toxicity for acids and metals can be evaluated independently (i.e., as the free metal and/or free acid).

Table 3. Comparison of acute toxicity values for C2 and C3 carboxylic acids and salt

Acute Mammalian Toxicity	**Acetate**	**Propionate**
Acute oral toxicity (LD50 in mg/kg bw)	4960	2600-4290
Acute inhalation toxicity (LC50 in mg/L)	11.4	>4.9
Acute dermal toxicity (LD50 in mg/kg bw)	1060	500

Bioequivalency of Metal Carboxylates

Evaluation of the "bioaccessability" (an estimate of bioavailability) of cobalt compounds, including two cobalt carboxylates and cobalt chloride has been reported by Stopford et al. (2003) and similar evaluation of bioequivalency" has been reported by Firriolo (1992). While not specifically conducted with any of the compounds in this category, the work of these authors has direct relevance because of their common metal cation, cobalt and similarities of their dissociation constants with those of compounds in this category. Similar results would be expected for the compounds in the current category being discussed. Stopford et al. (2003) investigated the solubility of these two cobalt carboxylates and cobalt chloride (when added as fine powders) in synthetic fluids designed as surrogate gastric juices. These investigators showed that these cobalt salts were completely dissociated and dissolved at a gastric pH (1.2) (Table 4). When added to surrogate intestinal fluids at neutral pH (7.4), $Co(II)Cl_2$ was also highly soluble. The solubility of the cobalt (% available cobalt expressed as Co(II) ion) in cobalt carboxylates ranged from 30.8 to 50.8 percent available cobalt at 72 hours (Table 4). These results for cobalt chloride and cobalt naphthenate are highly consistent with data reported by Firriolo 1992 for these same salts in similar surrogate biological fluid matrix (Table 4). Maximum solubility of Co naphthenate was observed at 48 hrs, which was the longest sample time used in the study.

These bioequivalency data are valuable for two reasons. They confirm the prediction from the dissociation studies that these compounds are expected to be completely dissociated in the gastrointestinal tract (low pH) and a substantial proportion of these compounds would be expected to be dissociated and bioavailable in water at neutral pH (7.4).

Table 4: Results of Extraction of Cobalt from Surrogate Biological Fluids

Matrix (pH)	**Maximum Solubility (% of available metal)**			
	$CoCl_2$	Co 2-ethyl-hexanoate	Co naphthenate	Co neodecanoate
Gastric pH (1.5)[a]	100	100	100	100
Gastric pH (2.0)[b]	100		100	--
Intestinal pH (7.4)[a]	100	50.8*	45.4*	30.8*
Intestinal pH (7.3)[b]	85	--	20**	--

[a] From Stopford et al. (2003); [b] Firriolo (1992)

* Maximum concentration observed at 72 hours.

** Maximum concentration observed at 48 hours.

Stopford et al. (2003) and Firriolo (1992) added all of the salts to the neutral (intestinal) surrogate solutions as finely ground powder. It is not surprising that the percent of available cobalt from cobalt carboxylates appears to increase with time (48 or 72 hours). Firriolo (1992) also evaluated the solubility of ground and ethanol-solubilized cobalt naphthenate in a neutral buffer solution[1]. For ground

[1] PBS = phosphate buffered solution without $CaCl_2$ or $MgCl_2$

cobalt naphthenate, 20% of available Co(II) was dissociated. In contrast, 90% of available cobalt was observed as dissociated Co(II) when originally introduced in ethanol. The ethanol-solubilized Co(II) remained in solution. This finding has implications for dissociated Co(II) introduced to the intestine solubilized in gastric juices.

Cobalt is absorbed primarily as the free Co(II) ion via biochemical mechanisms at the intestinal mucosal wall (Firriolo 1992). Having been reported as completely soluble in gastric fluids (Stopford et al. 2003; Firriolo 1992) that Co(II) should remain soluble (100% dissociated Co(II)) after entering the intestine from the stomach. Once solubilized, this cobalt would be expected to undergo the same fate irrespective of the salt originally ingested. Stopford et al. (2003) emphasized the importance of confirming the interpretation of *in vitro* solubilities in surrogate fluids with *in vivo* data. In fact, Firriolo used these (Table 4) *in vitro* solubility tests as preliminary studies for subsequent comparative absorption, distribution and elimination studies. Discussion of *in vivo* data is presented in the following section.

Finally, the work by Stopford et al. (2003) shows that the metal chloride is similar to, or more bioavailable than, the corresponding metal carboxylate salts (Table 4), which makes the chloride a conservative surrogate when attempting to estimate the bioavailability and toxicity of dissociated metal salts. For this reason, data for the chlorides of cobalt has been emphasized during preparation of the attached robust summaries and is the preferred surrogate for the metal dissociation products of the two metal carboxylate salts in this catagory (Table I).

Comparative Toxicity and Pharmacokinetics

Toxicity data for soluble cobalt salts indicate that the contribution of the respective anion to the toxicity of the compound is negligible compared with that of the cobalt cation. Speijers et al. (1982) investigated the acute oral toxicity in rats of a series of cobalt compounds including cobalt acetate. Lethal doses varied significantly when calculated in terms of the compound weight; however, when based on the dose of the Co(II) ion, all of the LD50 values were within a factor of about two for all of the compounds (Table 5). With the exception of the fluoride and bromide salts, all other salts tested had LD50 values within the range from 140 to 190 mg Co/kg bw. The LD50 for cobalt acetate was in the middle of this range at 168 mg Co/kg bw. This work indicates that toxicity is related to the cobalt ion and independent of counter ions. Similar results would be expected for the salts in this category and carboxylate salts of higher molecular weight where the metal cation is much more toxic than the acid moiety[2].

[2] Where the anion of the salt is essentially nontoxic (e.g., sodium, calcium), the toxicity of the compound as a whole will be due to the toxicity of the acid component.

Table 5. A comparison of acute oral toxicity values of cobalt compounds calculated based on the weight of each compound or on the cobalt content of each respective compound.

Compound	LD50* (mg compound /kg bw)**	LD50* (mg Co/kg bw)
Cobalt(II) fluoride	150	91
Cobalt(II) oxide	202	159
Cobalt(II) phosphate	387	187
Cobalt(II) bromide	406	109
Cobalt(II) chloride	418	190
Cobalt(II) sulphate	424	161
Cobalt(II) nitrate	434	140
Cobalt(II) acetate	503	168

* Data from Speijers et al. (1982)
** Several test compounds were hydrates and contained water. Results are expressed based on the weight of the anhydrous compound.

This toxicity data is supported by evaluation the absorption, distribution, and elimination of cobalt following exposure to different metal salts. Work by Firriolo et al. (1999) showed that regardless of whether the compound was introduced as Co(II) chloride or Co naphthenate the absorption, disposition, and elimination of cobalt was the same. This data indicates that the carboxylic acid portion of the salt does not play a role in cobalt ion absorption *in vivo* once the compound (ion pair) has dissociated. These authors state that absorption of cobalt in the GI tract is dependent upon release of free metal ion and their results indicate that the acid, in this case naphthenate, does not limit the degree of absorption.

Firriolo et al. (1999) confirmed previous findings that cobalt absorption occurs in the jejunum of the small intestine. Working with intestinal rings, these authors showed that absorption of cobalt occurred via biochemical processes that occurred at the intestinal mucosal wall. These processes appear to be saturable and both concentration and temperature dependent (Firriolo 1992). These characteristics are indicative active transport (Ashmead et al., 1985 and Firriolo et al. 1999). In addition, there appears to be a diffusional component to the absorption of cobalt ions, which is also concentration dependent (Firriolo et al. 1999). Despite the presence of these mechanisms for cobalt absorption, uptake from the gut is incomplete. Only limited absorption of ingested cobalt occurs (e.g., 20% – 30%) in the gut (Firriolo 1992; ASTDR, 2001).

The *in vivo* toxicity (Speijers et al. 1982) and absorption/distribution data (Firriolo et al. 1999) are supported by the *in vitro* data for a broader range of cobalt carboxylates (Stopford et al., In press; Firriolo 1992; Firriolo et al. 1999). This body of work shows that the hazard of these metal carboxylates is largely dependent on the metal, and not the carboxylic acid. This facilitates the use of toxicity data for soluble metal salts (e.g., $Co(II)Cl_2$) that dissociate rapidly and

completely under physiological conditions, to estimate the potential hazard of the two metal carboxylates in this category.

SUPPORTING DATA FOR DISSOCIATION PRODUCTS

1. Data for the parent compounds (i.e., the metal carboxylate salts in the category) are provided in robust summary format. A set of robust summaries for each of the two metal carboxylate compounds are provided in a Appendices A and B to this document.

2. In addition, when available, data for the dissociation products (metals and carboxylic acids) are provided.

    a. Metal data gathered from established compendia such as ATSDR and WHO documents and specific key articles from the literature are summarized in the following sections and Tables I, II, III, and IV and presented in Appendix C.
    b. Carboxylic acid data is provided in the respective parent robust summary in the "Remarks" section, for each data element.

Acids

When available, robust summaries for acetate and propionate acids have been provided as appendices to the robust summaries for each respective salt. In addition these data are summarized and referenced in the appropriate remarks sections for each data element in the robust summaries of the respective metal carboxylate. Data for each of the acids is also summarized along with other existing data for the two C2 and C3 metal carboxylate salts and their dissociation products in Table I.

Metals:

The Coalition has relied upon well recognized and peer reviewed compendia (e.g., ATSDR Toxicological Profiles, WHO Environmental Health Criteria) for data on cobalt. Data for the soluble/dissociable forms of the metal (free metal or the chloride salt) are summarized (Appendix C) and discussed below along with other existing data in Tables I, II, and III, and IV. These well known compendia for metals are not provided with this submission, consistent with discussions with the EPA. These are readily available for EPA to review with this submission; however, where data is from the open literature copies of the reports are provided.

In summary, the key points relative to the two metal carboxylates in this category are:

- A common structure of $[RCOO^-]_2$ and an associated divalent metal cation;
    - RCOOH moieties for metal carboxylates in this category have R substituents of one or two carbons.
    - The common metal cation is cobalt.
- Dissociation constants (pK values) in the circum neutral range;
    - Complete or nearly complete dissociation at gastric pH (1.5 to 2.0);
    - Substantial dissociation at environmental pH (>30%);
- Metal carboxylates in this category have the same use pattern and function, to provide free metal ion to chemical reactions.

C2 AND C3 METAL CARBOXYLATES AND DISSOCIATION PRODUCTS

Metal: Cobalt

Cobalt

Cobalt is a naturally-occurring element that has properties similar to those of iron and nickel. It is an essential element, required for good health in animals and humans (ASTDR, 2001). A biochemically important compound containing cobalt is vitamin B_{12} or cyanocobalamin. For most people, food is the largest source of cobalt intake. The average person consumes about 11 micrograms of cobalt per day in their diet (ASTDR, 2001). Part of this cobalt comes from vitamin B_{12}, which is found in meat and dairy products. Cobalt is also found in surface and groundwater. In the U.S., concentrations in water are usually between 1 and 10 μg/L (ppb), although they may be much higher in areas that are rich in cobalt-containing minerals or in areas near mining or smelting operations. In most drinking water, cobalt levels are less than 1 – 2 ppb (ASTDR, 2001).

Soluble forms of cobalt, such as cobalt(II) chloride (or cobaltous chloride), are most likely to be absorbed and cause systemic effects in humans. For this reason, this compound has often been used in absorption and toxicology studies to determine the potential hazard of cobalt exposures. When coming into contact with water and biological fluids, cobaltous chloride dissolves and releases cobalt

as a +2 ion. In general, it is the cobalt ion that is responsible for causing toxicity[3]. Because of this, in this document, the toxicity of cobalt(II) chloride (expressed in terms of the cobalt ion), is used as a surrogate for the toxicity of cobalt that is released through the dissociation of the two cobalt carboxylate compounds in this category (i.e., cobaltous acetate and propionic acid, cobalt(II) salt).

Approximately 13-34% of cobalt(II) chloride is absorbed in the gut of rats. Absorption may be increased in iron deficient individuals. The highest concentration of absorbed cobalt is in the liver and then the kidney. There is no accumulation of cobalt with age. Following oral exposure, cobalt is eliminated primarily in feces (the unabsorbed fraction) and secondarily in urine (the absorbed fraction). For cobalt(II) chloride, 70 - 80% of the administered dose is eliminated in the feces. Elimination is biphasic or triphasic. The terminal phase involves a very small residual level of cobalt and has a half-life in years (ATSDR, 2001).

Carboxylic acids

Acetate

Acetic acid (acetate) and seven of its salts (H^+, NH^{4+}, Ca^{2+}, Mg^{2+}, Mn^{2+}, K^+, Na^+) have been included in the Carboxylic Food Acids and Salts Category under the HPV Challenge Program. Robust Summaries for these compounds have been prepared and submitted by the Acetic Acid and Salts Panel of the American Chemistry Council. The database for these compounds is quite complete and no additional testing was proposed under the HPV Challenge Program. The chemical structures, physical-chemical properties, environmental fate behavior, and aquatic and mammalian toxicity of the seven compounds are similar. Acetic acids and its salts undergo dissociation in aqueous media into the acetate anion and the respective cations. The toxicity of each compound is driven by acetate, with these non-toxic cations (not including cobalt) in most cases playing only a minor role.

Propionate

Propionic acid, also known as propanoic acid, and three of its salts (Ca^{2+}, Na^+, K^+) are common food additives used as mold inhibitors, preservatives, and flavoring agents. Propionates are metabolized and utilized in the same way as a normal fatty acid (JECFA, 1962). The safety of these compounds for use in food has been evaluated several times by the Joint FAO/WHO Expert Committee on

[3] Insoluble compounds that do not release significant amounts of the cobalt ion are much less toxic when administered orally (ASTDR, 2001). The oral toxicity of soluble cobalt compounds is similar when expressed in terms of the cobalt ion.

Food Additives. The Committee has concluded as recently as 1997 that there was no safety concern for these compounds at the current levels of use and that their Acceptable Daily Intake (ADI) need not be limited. The toxicology evaluation for these compounds concluded that there is no reason to believe that the propionic acid differs toxicologically from its calcium and sodium salts (JECFA, 1966).

EXISTING DATA FOR C2 AND C3 METAL CARBOXYLATE SALTS AND DISSOCIATION PRODUCTS

Physical-chemical Properties

Available physical-chemical property data for the compounds in this category and their dissociation products are shown in Table I and briefly summarized below.

Cobalt (as cobaltous chloride)

Not all of the physical-chemical properties of cobalt(II) chloride have been characterized. The compound has a melting point of 724°C and is highly soluble in water (450 g/L). Data are not available for its partition coefficient, vapor pressure, or Henry's law constant.

Carboxylic Acids

Acetate

Acetic acid is highly soluble in water and relatively volatile. It readily dissociates in water and has a pKa of 4.76.

Propionate

Propionic acid is miscible in water and has a dissociation constant (pKa) that is very similar to that for acetic acid (i.e., 4.8)

Metal Carboxylates

Physical-chemical property data for the carboxylate salts in this category are only partially complete. The salts either are or are expected to be quite soluble in water and have low octanol/water partition coefficients (i.e., log Kow <1).

Environmental Fate and Transport

Available environmental fate and transport data for the compounds in this category and their dissociation products are shown in Table II and briefly summarized below.

Cobalt (as cobaltous chloride)

Due to its high solubility in water and inorganic nature, cobalt(II) chloride is expected to be highly stable in water.

Carboxylic Acids

Acetate

Acetic acid is readily biodegradable and does not persist for long periods in water. In air, 50% is expected to degrade after 21 days.

Propionate

Propionic acid is readily biodegradable and does not persist for long periods in water.

Metal Carboxylates

The calcium salt of propionic acid is readily biodegradable and, as is the case for the acid, does not persist for long periods in water. Environmental fate data for the two cobalt salts is not available.

Ecotoxicity

Available ecotoxicology data for the compounds in this category and their dissociation products are shown in Table III and briefly summarized below.

Cobalt (as cobaltous chloride)

Cobalt(II) chloride has a low to moderate acute toxicity to fish (96-h LC50 = 1.4 mg Co/L for rainbow trout to 333 mg Co/L for carp) and a low to moderate acute toxicity to aquatic invertebrates (48-h EC50 values for *Daphnia magna* range from 1.11 to 5.6 mg Co/L). Acute toxicity to aquatic plants is also moderate (96-h EC50 for *Chorella vulgaris* = 0.522 mg Co/L).

Carboxylic Acids

Acetate

Acetic acid is of low to moderate toxicity to fish, invertebrates and algae. The toxicity of the acid appears to be mainly due to the effects of low pH, as toxicity is greatly reduced under neutralized conditions.

Propionate

Propionic acid is of low to moderate toxicity to fish, invertebrates and algae. As was the case for acetic acid, the toxicity of the acid appears to be mainly due to the effects of low pH, as toxicity is greatly reduced under neutralized conditions.

Metal Carboxylates

The calcium salt of propionic acid has very little toxicity toward aquatic organisms. Toxicity is much less than by the acid alone, supporting the fact that the toxicity of the acid is mainly due to the effects of low pH.

Mammalian Toxicity

Available mammalian toxicity data for the compounds in this category and their dissociation products are shown in Table IV and briefly summarized below.

Cobalt (as cobaltous chloride)

There are extensive toxicity data available for cobalt (II) chloride and several other soluble and insoluble salts of cobalt. These data have recently been compiled in a toxicological profile prepared by the Agency for Toxic Substances

and Disease Registry (ATSDR, 2001). In addition, the International Agency for Research on Cancer (IARC) has evaluated the carcinogenicity of cobalt and cobalt compounds (IARC, 1991). Significant findings for cobaltous chloride are presented below.

The single-dose rat LD50s for cobalt(II) chloride (expressed in terms of the cobalt +2 ion) range from 140 to 190 mg Co/kg bw[4]. For the mouse, the LD50 value expressed as the cobalt ion is 89.3 mg Co/kg. Acute dermal and inhalation toxicity data are not available for cobalt(II) chloride.

Repeated oral dosing of rats with cobalt chloride at levels ranging from 0.5 to 30.2 mg Co/kg/day for periods ranging from 12-16 days up to 7 months resulted in the following observations associated with LOAELs: reduced weight gain, increases in some organ weights (heart, liver and lungs); increased hematocrit, hemoglobin, and RBCs; renal tubular necrosis; and various changes on cardiac physiology (left ventricular hypertrophy, impaired ventricular function, and degeneration of myofibrils). Cardiac effects were observed in rats at LOAEL's ranging from 8.4 to 12.4 mg Co/kg/day, for cobalt sulfate or cobalt chloride, with exposure periods of 3 weeks to 6 months.

Cobalt compounds, including salts, have sometimes been observed as genotoxic or mutagenic when studied in *in vitro* test systems (Lison et al., 2001). Clastogenicity has also been demonstrated in mammalian cells; however, evidence of genotoxicity in humans is lacking.

Cobalt compounds with a valent state of II, the form of cobalt released by dissociation of cobalt salts in this category, are reported to be generally non-mutagenic in bacterial assays, but increased frequency of genetic conversions have been reported in yeast.

In a single developmental toxicity study with cobalt chloride exposure (5.4 or 21.8 mg Co/kg/day) from gestation day 14 to lactation day 21 the LOAEL was based on stunted pup growth. However, maternal toxicity was observed in conjunction with effects on the offspring and the growth effect was considered to be a secondary or indirect effect rather than a direct effect of cobalt on the fetus. No teratogenic effects were observed. Another study in rats provided a NOAEL of 24.8 mg Co/kg/day for cobalt chloride exposure from gestation days 6-15. No effects on fetal growth or survival in mice exposed to 81.7 mg Co/kg/day as cobalt chloride during gestation days 8-12 (Appendix C).

Reproductive effects were observed with extended exposures in water or diet. Testicular degeneration and atrophy have been reported in rats exposed to 13.2 to 30.2 mg Co/kg/day as cobalt chloride for 2-3 months in the diet or drinking water. Similar effects were seen in mice exposed to 23 to 43.4 mg Co/kg/day as

[4] This range does not include the two cobalt halogen compounds, CoF and CoBr, because they are much more reactive than the carboxylic acids and simple salts being evaluated here.

cobalt chloride in drinking water for 10-13 weeks. In addition, reduced numbers of pregnant females and pups per litter, and reduced fertility, were observed in mice exposed to 58.9 mg Co/kg/day.

The US National Toxicology Program does not recognize cobalt as a human carcinogen, however, IARC has classified cobalt and cobalt compounds as possibly carcinogenic to humans (Class 2B) based on sufficient evidence that cobalt metal powder and cobaltous oxide are carcinogenic in animals (IARC, 1991). We do not believe this is relevant to the cobalt compounds in this category (Appendix C).

Carboxylic Acids

Acetate

Acetic acid is a naturally occurring acid in many foods so there is a relatively extensive mammalian toxicity database available for this compound (Table IV). This acid has a low acute toxicity (LD50 = 4,960 mg/kg bw). Long-term exposure by intubation causes hyperplasia of the esophagus and fore-stomach, likely due to the acidity of the compound (sodium acetate given in drinking water does not produce this effect). Acetic acid is not mutagenic and did not cause developmental toxicity after maternal oral doses up to 1,600 mg/kg bw/day.

Propionate

Propionic acid is a normal intermediary metabolite in animals and humans. There is an extensive mammalian toxicity database available for this compound. The acid has a low acute and chronic toxicity in animal studies (Table IV), although it is corrosive and irritating to skin and eyes. It is not mutagenic in either *in vitro* or *in vivo* studies. Most of the effects of the compound are believed to be due to the acidity of the compound rather than its systemic toxicity.

Metal Carboxylates

There are limited mammalian toxicity data for cobalt(II) acetate. Acute toxicity data indicate that it is of similar toxicity to cobalt chloride when expressed in terms of the cobalt(II) ion alone (LD50 = 168 vs. 190 Co mg/kg bw)(Speijers et al., 1982). Cobaltous acetate gave a very weak to weak positive result in an *in vitro Salmonella* mutagenicity assay, but was negative in an *in vivo* mouse micronucleus assay (Table IV). The salt was not teratogenic in several developmental toxicity studies.

There are no available mammalian toxicity data for the cobalt(II) salt of propionic acid.

TEST PLAN: METAL SALTS OF C2 AND C3 CARBOXYLATES CATEGORY:

Cobalt Salts of Acetates and Propionates	*CAS#*
Cobalt Acetate	71-48-7
Propionic Acid, Cobalt Salt	1560-69-6

The Test Plan for the Cobalt Salts of C2 and C3 Carboxylates Category is presented in Table 1. Justification of the test plan is based upon existing data as summarized in the category justification above and in Tables I, II, III, and IV.

PHYSICOCHEMICAL PROPERTIES:

Melting point, boiling point, and water solubility, have been recently determined for Co acetate and Co propionate. This data is included in Table I and in Appendices A and B. All studies are being conducted for each compound (Table I). Dissociation studies (OECD Guideline 112) have also recently been conducted for both compounds. This data is presented in Table I(above), the robust summaries and thoroughly discussed in the text. The partition coefficient study was not conducted for either of the carboxylates in this category, because this is inappropriate for ionizeable and dissociable compounds.

ENVIRONMENTAL FATE PARAMETERS:

Adequate biodegradation data are currently available for the two acid components of the salts in this subcategory (i.e.. acetate and propionate). These acids rapidly biodegrade. The organic portions of the two cobalt salts are also expected to degrade, provided ambient concentrations are not so high that cobalt toxicity to microorganisms becomes an issue. Therefore, to supplement the existing biodegradation information, additional biodegradation data will be generated for Co acetate to determine the effect, if any, that the Co(II) ion will have on the biodegradation of the organic portion of this compound under ambient conditions. Of the two cobalt-containing compounds in the category, Co acetate has the highest ratio of metal weight to total compound weight and would, therefore, represent the worst case for potential cobalt exposure. Data from this study, as well as bacterial inhibition data from the scientific literature, will be used estimate concentrations where cobalt propionate might be expected to cause microbial inhibition and thus reduce inherent biodegradation. Transport data was available for Co acetate and Co propionate and were calculated using SAR and standard fugacity models (e.g., EPIWIN 3.11)

ECOTOXICITY

Sufficient data are available for the dissociation products of Co acetate and Co propionate (i.e., cobalt ion, acetate, and propionate); however, ecotoxicity data for the two cobalt salts are currently lacking. Acute aquatic toxicity testing with fish, daphnia and algae is therefore proposed for both Co acetate. Data is available for both dissociation products for Co propionate and a daphnia acute study will be conducted to confirm that under ambient environmental conditions (i.e., neutral pH), the compound is not more toxic than would be predicted from the existing data for its dissociation products. Using the Henderson Hasselbalch equation, the proportion of Co (II) ion will be calculated using the pH of the test system and the pKa of the salt, and toxicity values will be expressed based on free Co(II) ion concentration as well as the salt. This data will then be compared directly to cobalt compound toxicity data also expressed in terms of the cobalt (II) ion. Conduct of four aquatic studies will allow us to determine whether or not the undissociated ion pair contributes to the toxicity of the compound as a whole under ambient conditions.

HUMAN HEALTH EFFECTS

Acute toxicity studies

Acute oral toxicity data is available for the dissociation products including acetic acid, propionic acid, and cobalt as Co(II) chloride. Acute oral toxicity data is also available for Co acetate. As shown in Table 3 and Table IV, the LD50 values for acetic acid and propionic acid and propionic acid calcium salt are very consistent with each other (Table 3). The LD50 value for cobalt acetate, when expressed on the Co(II) content (168 mg Co/kg bw) is very similar to that for Co (II) chloride (190 mg Co/kg bw) generated in the same study (Speijers et al. 1982). To further confirm the result so Speijers et al. (1982) and the contention that toxicity is due to the cobalt ion, the Coalition proposes to conduct an additional acute oral toxicity study in rats with Co propionate. This data is important to developing and supporting the category strategy.

Genotoxicity studies

No additional genetic toxicity studies are proposed. Existing data for the dissociation products are acetate and propionate are all negative (Table IV). Adequate genetic toxicity data are also available for cobaltous acetate. The genotoxicity of cobalt propionate can be nferred from existing data for inorganic soluble cobalt salts and cobalt acetate (Table IV).

Higher-tiered toxicity studies

The hazard for higher tiered mammalian toxicity data elements (repeated dose, reproduction and developmental), can be estimated from existing data for the salts and dissociation products. This includes acute toxicity data and existing chronic data on the acetate, propionate and cobalt (see Table I (d) and Table IV). As discussed in detail in the Category Justification (above), the oral toxicity of the cobalt carboxylate salts is determined primarily by the toxicity of the metal ion (i.e., Co (II)) and is independent of the carboxylate substituent. This is supported by comparing the acute toxicity to cobalt acetate with the acute toxicity of Co(II) chloride when both are expressed based on Co (II) ion (Speijers 1982). The respective LD 50 values of 168 and 190 mg Co/kg bw are equivalent. This indicates that the toxicity to the metal as acetate and chloride is essentially the same, while data for the respective acids, acetate and propionate, have a much lower order of toxicity compared to Co Chloride (Table IV). This will be further supported by the results of the acute study proposed for Co propionate.

Higher tiered mammalian studies based upon dietary or oral exposure are simply repetitive acute exposures to the metal ion (i.e., Co(II)); therefore, the toxicity in these higher tiered studies can be estimated based upon metal (Co(II)) data. In this category, the only metal of toxicological significance is cobalt. This premise is supported by comparing the existing data for repeated dose and developmental studies for acetate and propionate salt to the existing data for cobalt for these end points (Table IV). Data for the carboxylic acid and dissociation products for repeated dose and developmental end points are approximately 5 to 50 fold and 20 to 300 fold, respectively, less toxic than the reported values for Co(II) (Table IV). For these reasons, no additional studies for higher tiered mammalian studies are proposed. Repeated dose, developmental and reproductive hazard of Co acetate and Co propionate can be estimated based primarily on existing cobalt data.

Test Plan Matrix: C2 and C3 Metal Carboxylates of Cobalt

Data Elements	Co acetate			Co propionate			Dissociation products			Test Recommendations	
	Information available	GLP Study	Acceptable	Information available	GLP Study	Acceptable	Acetate	Propionate	Cobalt	Cobalt Acetate	Cobalt Propionate
PHYSICOCHEMICAL PROPERTIES											
Melting Point	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N
Boiling Point	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N
Vapor pressure	N	N	N	N	N	N	N	Y	NA	N	N
Partition Coefficient	NA	-	-	NA	-	-	Y	Y	NA	N	N
Water Solubility	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N
ENVIRONMENTAL FATE PARAMETERS											
Photodegradation	N	N	N	N	N	N	Y	Y	NA	N	N
Dissociation in water	Y	Y	Y	Y	Y	Y	Y	Y	NA	N	N
Transport	Y	N	Y	Y	N	Y	Y	N	NA	N	N
Biodegradation	N	N	N	N	N	N	Y	Y	NA	Y	N
ECOTOXICITY											
Fish toxicity (96-h)	N	N	N	N	N	N	Y	Y	Y	Y	N
Invertebrate toxicity (48-h	N	N	N	N	N	N	Y	Y	Y	Y	N
Algae toxicity (72-h)	N	N	N	N	N	N	Y	Y	Y	Y	N
TOXICITY											
Acute Oral LD50, rat	Y	NS	Y	N	N	N	Y	Y	Y	N	Y
Repeated dose	N	NS	N	N	N	N	Y	Y	Y	N	N
Genetic Toxicology – (*in vitro*) mutation assay	Y	NS	Y	N	N	N	Y	Y	Y	N	N
Genetic Toxicology – (*in vitro*) chromosomal aberration	Y	NS	Y	N	N	N	Y	Y	Y	N	N
Genetic Toxicology – (*in vivo*)	Y	NS	Y	N	N	N	N	Y	Y	N	N
Reproductive	N	N	N	N	N	N	N	N	Y	N	N
Developmental	Y	N	Y	N	N	N	Y	N	Y	N	N

Y = yes; N = No; NA = not applicable; NS= not specified;

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APPENDIX A

COBALT ACETATE ROBUST SUMMARIES

APPENDIX A1

ACETIC ACIDS AND SALTS CATEGORY: ROBUST SUMMARIES

APPENDIX B

COBALT PROPIONATE ROBUST SUMMARIES

APPENDIX B1

IUCLID 2000: PROPIONIC ACID

APPENDIX C

COBALT CHLORIDE ROBUST SUMMARIES

AR201-13102

COURTNEY M. PRICE
VICE PRESIDENT
CHEMSTAR

American Chemistry Council
Good Chemistry Makes It Possible

June 28, 2001

Honorable Christine T. Whitman
Administrator, U.S. EPA
P.O. Box 1473
Merrifield, VA 22116

RE: Chemical Right-to-Know Program - Assessment Plan and Robust Summaries for the Acetic Acid and Salts Category, Registration Number

Dear Administrator Whitman:

The American Chemistry Council Acetic Acid and Salts Panel (Panel) submits for review and public comment its assessment plan report and robust summaries for the Acetic Acid and Salts Category under the U.S. Environmental Protection Agency's (EPA) High Production Volume Chemical Challenge Program. The Panel members are listed in the assessment plan report. Included in this package is a computer diskette that contains electronic copies of the assessment plan and robust summaries.

The Panel understands that there will be a 120-day review period for the assessment plan report and that all comments generated by, or provided to, EPA will be forwarded to the Panel for consideration.

Thank you in advance for attention to this matter. If you have any questions regarding the assessment plan report or robust summaries, please contact Laurie Miller, the Panel Manager. She can be reached at 703-741-5611 (telephone), 703-741-6091 (telefax) or laurie_miller@americanchemistry.com (email).

Sincerely yours,

MR 49480

U.S. HIGH PRODUCTION VOLUME (HPV) CHEMICAL CHALLENGE PROGRAM

ASSESSMENT PLAN

For

ACETIC ACID AND SALTS CATEGORY

Prepared by
American Chemistry Council
Acetic Acid and Salts Panel

June 28, 2001

TABLE OF CONTENTS

I. INTRODUCTION

The High Production Volume (HPV) Challenge Program is a voluntary initiative with an objective of completing screening level hazard data profiles for approximately 2800 HPV chemicals as identified on the US Environmental Protection Agency's (USEPA) 1990 Toxic Substances Control Act (TSCA) Inventory Update Rule (IUR). In the US, HPV chemicals are those that are manufactured or imported in quantities greater than 1 million pounds per year. The hazard data to be provided in the program are those that meet the requirements of the Screening Information Data Set (SIDS) Program (OECD 1997a). SIDS, which has been internationally agreed to by member countries of the Organization for Economic Cooperation and Development (OECD), provides the basic screening data needed for an initial assessment of the physical-chemical properties, environmental fate, and human and environmental effects of chemicals. The information for completing the SIDS can come from existing data, may be generated as part of the HPV Challenge Program or may be provided through structure activity or category-based analyses. Once the available studies are identified or conducted, "robust summaries" are prepared.

The USEPA, Industry, and Non-Governmental Organizations (NGOs) are unified in their commitment to minimize the numbers of animals tested in the HPV Challenge Program whenever it is scientifically justifiable (USEPA 1999a, 1999b). Evaluating closely related chemicals as a group, or category, rather than solely as individual chemicals is one way to accomplish this goal. The use of categories is encouraged by USEPA in the HPV Challenge Program. Appropriately constructed categories allow for a more efficient evaluation while reducing the number of animals required for testing.

In accordance with the HPV Challenge Program, the Acetic Acid and Salts Panel (Panel), housed at the American Chemistry Council, is sponsoring a category that includes acetic acid and its salts as well as related acids and their salts. The Panel is comprised of the following companies:

A.E. Staley Manufacturing Company
Millennium Chemicals Incorporated
Cargill, Inc.
Archer Daniel Midland Company
The Procter and Gamble Company
Vulcan Chemicals
W.R. Grace & Company
Mallinckrodt Inc.
Eastman Kodak Company
Eastman Chemical Company
Sterling Chemicals
Celanese Ltd
OMG Americas, Inc.
The Shepherd Chemical Company

This assessment plan provides a summary and analysis of the available data, and identifies areas where additional data may be needed. Section II of this assessment plan provides a rationale and justification for the development of the Acetic Acid and Salts category. Section III reviews the methods used in the collection of published and unpublished data. Section IV reviews the evaluation of data quality. Section V reviews the preparation of the robust summaries and the construction of a data matrix. Section VI is an in-depth evaluation of data matrix patterns for each of the four data endpoint categories (i.e., physical-chemical properties, environmental fate, ecotoxicity and toxicity). Section VII is a summary of the Acetic Acid and Salts category and its properties. Section VIII presents the conclusions regarding data availability and the need for additional testing to complete the SIDS profiles for the sponsored compounds.

II. IDENTIFICATION OF THE STRUCTURE BASED CATEGORY

The Panel is sponsoring a total of 13 individual compounds, the structures of which are shown in Appendix 1. The category includes several food acids and their corresponding salts, specifically acetic acid and its ammonium, calcium, potassium, sodium, magnesium, and manganese salts; citric acid and its sodium, tripotassium and trisodium salts; fumaric acid; and malic acid[1]. These compounds are grouped together because of their close structural relationships, their natural occurrence in plants and animals, and their fundamental role in cell metabolism, particularly in the tricarboxylic acid cycle (also known as the citric acid or Kreb's cycle), which is where humans get their energy. These compounds are all carboxylic acids or their respective salts. As shown in Appendix 1, acetic acid has one, fumaric acid and malic acid have two, and citric acid has three carboxylic acid functional groups. Malic acid and citric acid also have an additional alcohol group.

Role in the Citric Acid Cycle

Food acids, such as acetic acid, citric acid, fumaric acid, and malic acid (and citrate, fumarate and malate), are found in a wide variety of unprocessed foods. The last three acids play key roles in the metabolic energy system called the Citric Acid Cycle or Kreb's Cycle (Gardner 1966). The cycle consists of a series of chemical reactions occurring within the cell that are responsible for the final breakdown of food molecules to form carbon dioxide, water, and energy. This process is active in all animals and higher plants and is carried out in the mitochondria.

The cycle is the major pathway by which animals obtain their required energy, and three of these food acids (citric, fumaric and malic) are integral components in this series of enzymatic reactions. A key feature of the cycle is that the citric, fumaric and malic acids are used over and over again in the production of energy. Furthermore, these acids catalytically accelerate oxygen uptake and the production of carbon dioxide by muscle and other tissues. They are not found in appreciable

[1] Note that the salts may be referred to by synonyms in some sources. For example, acetic acid ammonium salt is commonly called ammonium acetate. Similarly, citric acid tripotassium salt is commonly called potassium citrate (or tripotassium citrate).

quantities among the waste products, as elimination by animal kidneys tends to increase their consumption by the respiratory reactions, thus maintaining an "acid-base" balance within the animal system (Gardner 1966).

In summary, the compounds in this category are naturally occurring in foods and essential to normal metabolic processes. They are also commonly used as flavor and texture enhancers in a wide variety of foods. The compounds in this category can be viewed as biochemically and toxicologically equivalent to their naturally occurring counterparts.

III. COLLECTION OF PUBLISHED AND UNPUBLISHED DATA

Panel members contributed in-house studies of physical-chemical properties, environmental fate and transport, ecotoxicity, and mammalian toxicity for the compounds in the category. To supplement the industry data, literature searches were conducted of on-line databases and CD-ROMs (e.g., Hazardous Substance Data Bank [HSDB], Registry of Toxic Effects of Chemical Substances [RTECS], Aquatic Toxicity Information Retrieval [AQUIRE]), standard scientific compendia (e.g., *CRC Handbook of Chemistry and Physics*, *The Merck Index*, *Patty's Industrial Hygiene and Toxicology*, *Handbook of Environmental Data on Organic Chemicals*, BIBRA toxicology profiles), and other published sources (e.g., International Uniform Chemical Information Database [IUCLID]). The literature search was augmented by investigating the web sites of a variety of government and regulatory organizations, such as the Agency for Toxic Substances and Disease Registry (ATSDR), Consumer Product Safety Commission (CPSC), Food and Drug Administration (FDA), and World Health Organization (WHO). The USEPA ECOTOX database was also searched. A number of primary references from peer reviewed published journals were also reviewed. The Syracuse Research Corporation EPIWIN v.2.2 model, which is accepted by the U.S. Environmental Protection Agency (USEPA) for organic compounds, was used to provide estimates of key physical-chemical properties for some of the compounds.

IV. EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general USEPA and OECD SIDS guidance (USEPA 1999c; OECD 1997b) and the systematic approach described by Klimisch et al. (1997). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. The Klimisch et al. (1997) approach specifies four categories of reliability for describing data adequacy. These are:

1 **Reliable without Restriction:** Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

2 **Reliable with Restrictions:** Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

3 **Not Reliable:** Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

4 **Not Assignable:** Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

Only those studies which are deemed reliable for the current HPV Challenge Program purposes are included in the data set for this assessment plan. Reliable studies include both categories rated 1 (Reliable without restriction) and 2 (Reliable with restrictions). Studies rated 3 (Not reliable) were not used. Studies rated 4 (Not assignable) were used when professional judgment deemed it appropriate as part of a weight-of-evidence approach. Finally, some older studies were not included if they had been superceded by more recent studies rated 1.

V. ROBUST SUMMARIES AND CONSTRUCTION OF DATA MATRIX

Robust summaries were prepared according to the format recommended by the USEPA (1999d) and OECD (1997a) and constructed using Microsoft Word software. These summaries present the salient information from each of the reliable studies. All of the summaries are collected into a dossier that includes all of the individual acids and salts for the category. The dossier for the Acetic Acid and Salts category is a separate document that should be used in conjunction with this assessment plan.

The data in the robust summaries are used to construct a data matrix table. This table (Appendix 1 to this assessment plan) is a matrix of SIDS/HPV endpoints and the available data for each of the sponsored compounds in the Acetic Acid and Salts category. To facilitate the connection between data in the table and the corresponding robust summaries, reference sources have been included with each data point.

VI. EVALUATION OF MATRIX DATA PATTERNS

The data matrix table (Appendix 1) identifies where data for specific compounds and data endpoints are available (data provided) and not available (indicated by "--" in the table). The available data were evaluated for patterns and trends among the 13 compounds that could be used to predict values for a particular endpoint (e.g., acute oral toxicity) where adequate data are not available for a given compound (i.e., "Read Across"). In addition, the data were evaluated to determine to what extent the SIDS/HPV data endpoints were covered by available data for each compound in the category (i.e., "Read Down").

A. Evaluation of "Read Across" Patterns

The following discussion reviews the "Read Across" patterns among the 13 compounds for each of the four major data areas: physical-chemical properties, environmental fate and transport, ecotoxicity, and mammalian toxicity. The primary patterns to look for in the physical-chemical property data are similarities in the parameters that affect dissociation and partitioning between aqueous and organic phases. In reviewing the environmental fate data, the important information to look for is the primary mechanism of degradation or dissociation of the compounds. These factors also affect the bioavailability and aquatic toxicity of the compounds. Similarly, it is important to look for any trends or similarities in the mammalian toxicity data, which are important surrogates for potential human effects. Each of the four acids (acetic, fumaric, malic, and citric), along with their corresponding salts, are reviewed separately in the following sections.

Acetic Acid and its Salts

Acetic acid and its salts are comprised of seven compounds that include acetic acid ($H_4C_2O_2$), ammonium acetate ($H_7C_2NO_2$), calcium acetate ($H_6CaC_4O_4$), magnesium acetate ($H_6C_4MgO_4$), manganese acetate ($H_6C_4MnO_4$), potassium acetate ($H_3KC_2O_2$), and sodium acetate ($H_3NaC_2O_2$). The chemical structures, physical-chemical properties, environmental fate behavior, and aquatic and mammalian toxicity of these seven compounds are similar. Acetic acid and its salts undergo dissociation in aqueous media into the acetate anion ($H_3C_2O_2^-$) and the respective cations (H^+, NH_4^+, Ca^{2+}, Mg^{2+}, Mn^{2+}, K^+, Na^+). The toxicity of each compound is driven by acetate, with the cations playing a minor role.

Physical-chemical Properties

Reliable data exist for melting and boiling points, water solubility and pH for most of the seven compounds (see Appendix 1). With the exception of acetic acid, for which actual experimental data exist, octanol-water partition coefficient (Kow) and vapor pressure data are largely available as estimated values using the standard chemical property estimation software, EPIWIN v.2.2 (Syracuse Research Corporation 1993). All seven compounds are highly water soluble and of moderate to low volatility. Based on such information, the Panel believes that the available data adequately characterizes the physical-chemical properties of acetic acid and its salts.

Environmental Fate and Transport

Reliable data for environmental fate and transport behavior are available for acetic acid and its salts (see Appendix 1). Biodegradation appears to be the most significant removal mechanism. These compounds readily dissociate into their respective cations and the acetate anion; the anion is subsequently biodegraded. Data indicate that acetic acid and sodium acetate (acetic acid, sodium salt) photodegrade, although the rate is substantially slower than that of biodegradation. Level I fugacity modeling predicts that about 73% of any acetic acid

released to the environment would partition to water, with the remainder partitioning into the air. These data demonstrate that acetic acid and its salts are not persistent in the environment. The Panel believes that the available data and analogous behavior of the compounds can be used to adequately characterize the environmental fate and transport properties of acetic acid and its salts.

Ecotoxicity

Reliable ecotoxicity data for aquatic animals are available for four of the seven compounds (see Appendix 1). The ecotoxicity data indicate that these compounds are practically nontoxic to only slightly toxic. The three remaining salts (calcium, magnesium and manganese) are closely related to the other salts in structure and behavior and so would be expected to have low toxicity as well. Of the seven compounds, acetic acid appears more toxic, which is attributable to its relatively low pH. Toxicity data for algae are available for acetic acid and its sodium salt, and also indicate generally low toxicity. While some of these compounds lack actual data, the Panel believes that the available aquatic toxicity data and the generally low to moderate toxicity of acetic acid and its salts adequately characterize the ecotoxicity of these compounds.

Mammalian Toxicity

Several aspects of mammalian toxicity are evaluated. Acute testing provides information on gross effects, such as mortality, from exposure to high doses. Repeated dose testing provides information on toxicity associated with multiple doses over time. Genetic testing is conducted to evaluate the potential for mutagenic effects by using bacterial systems (e.g., the Ames test), non-bacterial systems (e.g., chromosomal aberrations), and *in vivo* (i.e., live animal) systems. Reproductive and developmental/teratogenic testing provides information on the potential effects of long-term exposure to lower doses, especially as related to possible effects in developing embryos and young animals. It is important to note that the lack of significant exposure may obviate the need to fill apparent data gaps with mammalian testing.

The available data indicate that acetic acid and its salts have generally low acute mammalian toxicity (see Appendix 1). Acute oral toxicity data for mammals are available for all compounds with the exception of the ammonium salt. Acute inhalation data are available for acetic acid and the sodium salt. Inhalation is not expected to be a primary route of exposure given that acetic acid and its salts have generally low volatility and are highly soluble. Dermal toxicity data are available only for acetic acid, but the level of toxicity is low and the salts are expected to exhibit a comparable dermal safety profile. Several studies indicate that the acute toxicity via other routes of exposure (i.e., intravenous, subcutaneous, intraperitoneal, etc.) is also low. Thus, additional acute testing on the other compounds is not deemed by the Panel to be necessary to characterize this category.

There are repeated dose, genetic, and developmental/teratogenic toxicity test endpoints for acetic acid. An essentially complete set of data for the sodium salt of acetic acid also is available. Less data are available for the other salts, but the data that are available show similar responses to the sodium salt. The dissociative nature of salts suggests that additional testing would provide no information useful for assessing the hazard of this category. Of note, none of the counter ions is expected to impact the overall safety profile of the salts within this chemical category.

In addition, acetic acid is naturally occurring as the acid in apple cider vinegar and other fruit-derived products. It and several of its salts are commonly used as food additives (e.g., as flavor enhancers) and are listed as Generally Recognized as Safe (GRAS) by the USFDA. Given the lack of significant toxicity, the natural occurrence in both plants and animals, and the common use in foods, the Panel believes that no additional mammalian toxicity testing is necessary.

Fumaric Acid

While acetic acid is the simplest form and contains only a single carboxylic acid unit, fumaric acid ($H_4C_4O_4$) contains two carboxylic acid units connected by a double bond.

Physical-chemical Properties

Reliable data are available for all of the SIDS/HPV data elements and indicate that fumaric acid is highly soluble in water and has low volatility. Level I fugacity modeling predicts that virtually all (99.8%) of any fumaric acid released to the environment would partition to water. The Panel believes that the available data adequately characterize the physical-chemical properties of fumaric acid.

Environmental Fate and Transport

Reliable data are available for all the SIDS/HPV data elements. Fumaric acid dissociates into H^+ and fumate ($H_3C_4O_4^-$) and fumate undergoes significant degradation by both biotic and abiotic mechanisms and is therefore not persistent. Nearly complete biodegradation was observed after 21 days under aerobic conditions. The Panel believes that the available data adequately characterize the environmental fate and transport properties of fumaric acid.

Ecotoxicity

Likewise, complete data are available for all the SIDS/HPV aquatic toxicity data elements. LC_{50} values for fish and *Daphnia* were greater than 200 mg/L. The value for the more sensitive algae was 41 mg/L. These data indicate that fumaric acid has low toxicity to aquatic animals and plants.

Mammalian Toxicity

Acute oral and dermal toxicity data indicate that fumaric acid is of low acute toxicity, with LD50 values from approximately 10 g/kg bw (oral) to greater than 20 g/kg bw (dermal). *In vitro* and in vivo studies were negative with regards to genetic toxicity. Reproductive and developmental/teratogenic toxicity studies also resulted in no indication of these effects after exposure to fumaric acid. The Panel believes that the large amount of available data and the low toxicity indicated are adequate to characterize the mammalian toxicity of fumaric acid.

In addition, fumaric acid is naturally occurring in apples, beans, carrots and other fruits and vegetables. It is also commonly used to control pH and produce light textures in such foods as cake, cookies and soft drinks. Fumaric acid is listed as GRAS by the USFDA.

Malic Acid

Malic acid ($H_6C_4O_5$) is very similar to fumaric acid, with the difference being the addition of a hydroxyl group (OH) and removal of a double bond.

Physical-chemical Properties

Reliable data are available for all of the SIDS data elements and indicate that malic acid is highly soluble in water and has a low volatility. Based on such information, the Panel believes that the available data adequately characterize the physical-chemical properties of malic acid.

Environmental Fate and Transport

Photodegradation and biodegradation data are available for malic acid and show that it dissociates into H+ and malate ($H_5C_4O_5^-$). Malate has been shown in a series of screening tests to biodegrade readily in soil and water. Level I fugacity modeling predicts that 100% of any malic acid released to the environment would partition to water. Based on such information, the Panel believes that malic acid is not persistent in the environment and is adequately characterized.

Ecotoxicity

Data on the aquatic toxicity of malic acid to daphnids are available. No data on toxicity to fish and algae were available, but the 48 hour LC_{50} for *Daphnia magna* was 240 mg/L, indicating a low level of aquatic toxicity. Given this data and the considerable aquatic toxicity data for the structurally related compounds in this category (e.g. acetic, fumaric and citric acids), no further aquatic tests are deemed by the Panel to be necessary.

Mammalian Toxicity

Acute data for the oral and intraperitoneal exposure routes are available for malic acid and indicate a low to moderate toxicity. Dermal toxicity data are not available for malic acid, but are expected to be comparable to the relatively low order of dermal toxicity associated with fumaric acid. *Both in vitro* and *in vivo* studies demonstrated no evidence of genetic toxicity. Developmental/teratogenic toxicity studies also resulted in no indication of these effects after exposure to malic acid. The Panel believes that the large amount of available data, combined with the low toxicity, are adequate to characterize the mammalian toxicity of malic acid.

In addition, malic acid occurs naturally as the major acid in apples, apricots, cherries, broccoli, carrots, potatoes, and many other fruits and vegetables. It is also commonly used as a flavor booster in candy, jelly, fruit drinks and ice cream. It is listed as GRAS by the USFDA.

Citric Acid and its Salts

Citric acid and its salts are comprised of four compounds, which include citric acid ($H_8C_6O_7$), sodium citrate ($H_7NaC_6O_7$), tripotassium citrate ($H_5K_3C_6O_7$), and trisodium citrate ($H_5Na_3C_6O_7$). The chemical structures and available data indicate that the physical-chemical properties, environmental fate behavior, and aquatic and mammalian toxicity of these four compounds are similar. As in the case of the other acids and salts in this category, citric acid and its salts undergo dissociation in aqueous media into the citrate anion ($H_7C_6O_7^-$) and the respective cations (K^+, Na^+). The toxicity of each compound is driven by citrate, with the cations playing a minor role. Therefore, where data are available for any of the compounds within this sub-category, they are considered by the Panel to be adequate to represent the entire group.

Physical-chemical Properties

Reliable data exist for all relevant physical-chemical properties for citric acid and its tripotassium and trisodium salts. These compounds are all highly water soluble and of moderate to low volatility. The Panel believes that the available data adequately characterizes the physical-chemical properties of citric acid and its salts.

Environmental Fate and Transport

Data on the environmental fate of citric acid and its trisodium salt are available. These data indicate that citric acid and its salts dissociate into their respective cations and the citrate anion, which is subsequently biodegraded. Studies indicate that citric acid and its trisodium salt are readily biodegraded (90-98% degradation after 48 hours). Level I fugacity modeling predicts that 100% of any citric acid released to the environment would partition to water.

Therefore, the existing data indicates that citric acid and its salts are not persistent in the environment. Collectively, these data are adequate, in the Panel's opinion, to characterize the environmental fate and transport properties of the group.

Ecotoxicity

Aquatic toxicity data for fish, *Daphnia* and algae are available for citric acid and its trisodium salt and indicate that these compounds have very low toxicity. With LC_{50} values ranging from 120 to 1,526 mg/L, citric acid is considered to be of low aquatic toxicity. The toxicity that is exhibited is most likely attributed to pH. The salts exhibit even less toxicity. The Panel believes that the available data and the structural similarities adequately characterize the ecotoxicity of citric acid and its salts.

Mammalian Toxicity

The available data indicate that citric acid and its salts have generally low mammalian toxicity. Oral toxicity data for mammals are available for citric acid and its sodium salt and demonstrate low toxicity. Dermal toxicity studies indicate that these compounds are moderate contact irritants. Acute toxicity from other routes of exposure (i.e., intravenous, subcutaneous, intraperitoneal, etc.) are available for all four of the citric acid and salts and confirm the low toxicity. Repeated dose studies available for citric acid and its sodium salt resulted in no adverse effects. *In vitro* bacterial studies were negative for genotoxicity for citric acid and its sodium and tripotassium salts. An *in vivo* cytogenetics study with citric acid also indicated no genetic toxicity. Finally, reproductive and developmental/teratogenic data are available for citric acid and its sodium salt. While body weight and survival time were effected at high doses of citric acid, no reproductive, developmental or teratogenic effects were observed in tests with either the citric acid or its sodium salt. The Panel believes that the available data and analogous structures and behaviors are adequate to characterize the toxicity for citric acid and its salts.

In addition, citric acid occurs naturally in all citric fruits, beans, tomatoes, and many other fruits and vegetables. It is also listed as GRAS by the USFDA and is one of the most widely used food additives, with uses in everything from soft drinks to cheese. A SIDS Initial Assessment Report (SIAR) for citric acid was presented at SIDS Initial Assessment Meeting (SIAM) 11 in January 2001 and its status was determined to be, "currently of low priority for further work."

B. Evaluation of "Read Down" Patterns

The "Read Down" patterns were considered among the four major data areas (physical-chemical properties, environmental fate and transport, ecotoxicity, and mammalian toxicity) for each of the 13 compounds. Complete data sets are available for the acetic, fumaric, malic and citric acids. Several of the salts of these acids also have relatively complete data sets. The category is characterized by

acids and their salts, all of which readily dissociate in solution. This dissociation is followed by relatively rapid biodegradation and/or utilization in living organisms. The available data suggest that the cationic portion of the salt (e.g., Ca^{2+}, Mg^{2+}, K^{+}, Na^{+}) does not significantly affect the relative toxicity of these compounds. Based on the similarities in structure and behavior, the widespread natural occurrence in many fruits and vegetables, and the long history of use as food additives, the Panel believes that no further testing is necessary to predict the environmental fate, ecotoxicity or mammalian toxicity of these compounds.

VII. SUMMARY OF ACETIC ACID AND SALTS CATEGORY

The 13 compounds in the category are acetic acid, its salts, and three structurally related acids (fumaric, malic, citric), as well as the salts of the citric acid. These compounds are grouped together because of their close structural relationships, their natural occurrence in plants and animals, and their fundamental role in cell metabolism, particularly in the tricarboxylic acid cycle (also known as the Citric Acid Cycle or Kreb's Cycle), which is where humans get their energy. These compounds are all carboxylic acids or their respective salts. They are all listed as GRAS by the USFDA and have widespread use as food additives.

The Panel believes the available information supports the following conclusions. All of these acids and salts are highly water soluble and have low to moderate volatility. They dissociate readily in solution and biodegrade rapidly or are utilized in the body. They are not persistent in the environment.

These compounds all exhibit relatively low toxicity to aquatic organisms, with any toxicity observed related to the effect of lowered pH. Likewise, these compounds all exhibit relatively low acute mammalian toxicity. Similarly, no significant effects were observed in genotoxicity, reproductive, and developmental/teratogenic testing.

VIII. CONCLUSIONS

The similarities in chemical structure and behavior of these 13 compounds, as well as the similarities found in the available testing data, support assessing these compounds under a single Acetic Acid and Salts category. The Panel believes that the available data sufficiently characterize the physical-chemical properties, environmental fate, ecotoxicity and mammalian toxicity of the group. Where reliable study data do not appear to exist, the missing values can be estimated using the available data of related chemicals within the group. In addition, these compounds have enjoyed widespread use as additives in a multitude of foods over many years. Therefore, based on the available data, the structural similarities, the natural occurrence, and the lack of significant toxicity, the Panel believes that no further testing is necessary to characterize the compounds included in this category. Support for this conclusion was provided in a review of the SIAR for citric acid at SIAM 11 in January 2001, where its status was determined to be, "currently of low priority for further work."

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APPENDIX 1

SUMMARY DATA TABLE FOR ACETIC ACID AND SALTS CATEGORY

U.S. HIGH PRODUCTION VOLUME (HPV) CHEMICAL CHALLENGE PROGRAM

ROBUST SUMMARIES

for

ACETIC ACID AND SALTS CATEGORY

Prepared by
American Chemistry Council
Acetic Acid and Salts Panel

June 28, 2001

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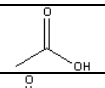
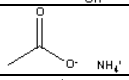
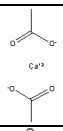
1. GENERAL SUBSTANCE INFORMATION

Robust summaries for the following substances are included in this Acetic Acid and Salts Category.

Chemical	CAS #	Structure
Acetic Acid	64-19-7	
Acetic Acid, Ammonium Salt	631-61-8	
Acetic Acid, Calcium Salt	62-54-4	
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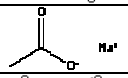
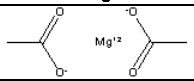
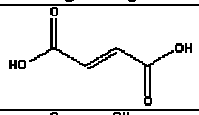
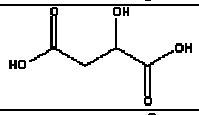
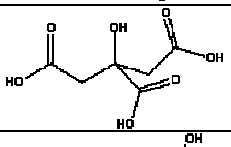
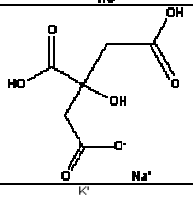
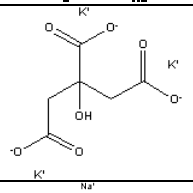
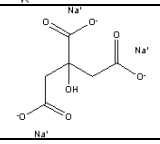
Acetic Acid, Sodium Salt	127-09-3	
Acetic Acid, Magnesium Salt	142-72-3	
Acetic Acid, Manganese Salt	638-38-0	
Fumaric Acid	110-17-8	
Malic Acid	6915-15-7	
Citric Acid	77-92-9	
Citric Acid, Sodium Salt	994-36-5	
Citric Acid, Tripotassium Salt	866-84-2	
Citric Acid, Trisodium Salt	68-04-2	

2. PHYSICAL-CHEMICAL DATA

2.1 MELTING POINT

(a)

Value:	16.7 °C
Decomposition:	Yes [ ] No [ ] Ambiguous [X]
Sublimation:	Yes [ ] No [ ] Ambiguous [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
References:	Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(b)

Value:	114 °C
Decomposition:	Yes [ ] No [ ] Ambiguous [X]
Sublimation:	Yes [ ] No [ ] Ambiguous [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Ammonium Salt (631-61-8)
References:	Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(c)

Value:	80 °C
Decomposition:	Yes [ ] No [ ] Ambiguous [X]
Sublimation:	Yes [ ] No [ ] Ambiguous [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Magnesium Salt (142-72-3)
References:	Budavari, S. (ed.). 1996. Merck Index. 12th ed. Whitehouse Station: Merck Research Laboratories.

(d)

Value:	292 °C
Decomposition:	Yes [ ] No [ ] Ambiguous [X]
Sublimation:	Yes [ ] No [ ] Ambiguous [X]

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid, Potassium Salt (127-08-2)
References: Lewis, R.T. (ed.) 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(e)
Value: 58 °C
Decomposition: Yes [ ] No [ ] Ambiguous [X]
Sublimation: Yes [ ] No [ ] Ambiguous [X]
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid, Sodium Salt (127-09-3)
References: Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(f)
Value: 287 °C
Decomposition: Yes [ ] No [ ] Ambiguous [X]
Sublimation: Yes [ ] No [ ] Ambiguous [X]
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Fumaric Acid (110-17-8)
References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(g)
Value: 128 °C
Decomposition: Yes [ ] No [ ] Ambiguous [X]
Sublimation: Yes [ ] No [ ] Ambiguous [X]
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Malic Acid (6915-15-7)
References: Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(h)

Value:	153 °C
Decomposition:	Yes [ ] No [ ] Ambiguous [X]
Sublimation:	Yes [ ] No [ ] Ambiguous [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)
References:	Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(i)

Value:	211 °C
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Sublimation:	Yes [ ] No [X] Ambiguous [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Calculated
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Citric Acid, Tripotassium Salt (866-84-2)
References:	Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(j)

Value:	150 °C
Decomposition:	Yes [X] No [ ] Ambiguous [ ]
Sublimation:	Yes [ ] No [X] Ambiguous [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* OECD Guideline 102
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
Remarks:	Decomposition begins at 150°C with water loss.
References:	European Commission. 1996. Trisodium Citrate. International Uniform Chemical Information Database.

2.2 BOILING POINT

(a)

Value:	118.1 °C
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)

References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(b)
Value: 160 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Remarks: Substance decomposes above the reported value.
Test substance: Acetic Acid, Calcium Salt (62-54-4)
References: Budavari, S. (ed.). 1996. Merck Index. 12th ed. Whitehouse Station: Merck Research Laboratories.

(c)
Value: > 400 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Remarks: Substance decomposes above the reported value.
Test substance: Acetic Acid, Sodium Salt (127-09-3)
References: Hoechst, A.G. 1993. Sicherheitsdatenblatt Natriumacetat entwaessert (04.03.1993). In European Commission. 1996. Sodium Acetate. International Uniform Chemical Information Database.

(d)
Value: 290 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Remarks: Sublimes.
Test substance: Fumaric Acid (110-17-8)
References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(e)
Value: 140 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Remarks: Substance decomposes above the reported value.
Test substance: Malic Acid (6915-15-7)

References: Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(f)
Value: Decomposes
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Citric Acid (77-92-9)
References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(g)
Value: 230 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Remarks: Substance decomposes when heated to the reported value.
Test substance: Citric Acid, Tripotassium Salt (866-84-2)
References: Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(h)
Value: Decomposes at red heat.
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Citric Acid, Trisodium Salt (64-08-2)
References: Lewis, R.J., Sr. 1994. Hawley's Condensed Chemical Dictionary. 12th Ed. New York: Van Nostrand Reinhold Co.

2.4 VAPOUR PRESSURE

(a)
Value: 15.2 hPa (11.4 mm Hg)
Temperature: 20 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid (64-19-7)

References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(b)
Value: 1.9 x 10^{-4} hPa (1.4 x 10^{-4} mm Hg)
Temperature: 25 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Calculated [X]; measured [ ]
GLP: Yes [ ] No [X] ? [ ]
Test substance: Acetic Acid, Ammonium Salt (631-61-8)
References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(c)
Value: 19.6 hPa (14.7 mm Hg)
Temperature: 25 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Calculated [X]; measured [ ]
GLP: Yes [ ] No [X] ? [ ]
Test substance: Acetic Acid, Calcium Salt (62-54-4)
References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(d)
Value: 9.44 x 10^{-7} hPa (7.08 x 10^{-7} mm Hg)
Temperature: 25 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Calculated [X]; measured [ ]
GLP: Yes [ ] No [X] ? [ ]
Test substance: Acetic Acid, Potassium Salt (127-08-2)
References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(e)
Value: 9.44 x 10^{-7} hPa (7.08 x 10^{-7} mm Hg)
Temperature: 25 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Calculated [X]; measured [ ]
GLP: Yes [ ] No [X] ? [ ]
Test substance: Acetic Acid, Sodium Salt (127-09-3)

References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(f)
Value: 2.05×10^{-4} hPa (1.54×10^{-4} mm Hg)
Temperature: 25 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Fumaric Acid (110-17-8)
References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(g)
Value: 6.1×10^{-6} hPa (4.6×10^{-6} mm Hg)
Temperature: 25 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Calculated [X]; measured [ ]
GLP: Yes [ ] No [X] ? [ ]
Test substance: Malic Acid (6915-15-7)
References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(h)
Value: 4.9×10^{-9} hPa (3.7×10^{-9} mm Hg)
Temperature: 25 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Calculated [X]; measured [ ]
GLP: Yes [ ] No [X] ? [ ]
Test substance: Citric Acid (77-92-9)
References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(i)
Value: 2.79×10^{-12} hPa (2.09×10^{-12} mm Hg)
Temperature: 25 °C
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Calculated [X]; measured [ ]
GLP: Yes [ ] No [X] ? [ ]
Test substance: Citric Acid, Tripotassium Salt (866-84-2)
References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(j)

Value:	2.79 x 10^{-12} hPa (2.09 x 10^{-12} mm Hg)
Temperature:	25 °C
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Calculated [X]; measured [ ] GLP: Yes [ ] No [X] ? [ ]
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
References:	Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

2.5 PARTITION COEFFICIENT logK_{ow}

(a)

Log Kow:	-0.17
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
References:	Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(b)

Log Kow:	-2.79
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Calculated [X]; measured [ ]
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Ammonium Salt (631-61-8)
References:	Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(c)

Log Kow:	-0.97
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Calculated [X]; measured [ ]
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Calcium Salt (62-54-4)
References:	Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(d)

Log Kow:	-3.72
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Calculated [X]; measured [ ]
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Potassium Salt (127-08-2)
References:	Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(e)

Log Kow:	-3.72
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Calculated [X]; measured [ ]
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
References:	Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(f)

Log Kow:	0.33
Temperature:	23 °C
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Fumaric Acid (110-17-8)
References:	Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(g)

Log Kow:	-1.26
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Malic Acid (6915-15-7)
References:	Hansch, C. and Leo, A. 1987. The Log P Database. Claremont, CA: Pomona College. In Hazardous Substances Databank (HSDB). Malic Acid. 1999. National Library of Medicine, Bethesda, MD.

(h)

Log Kow:	-1.72
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated

GLP: Yes [ ] No [ ] ? [X]
Test substance: Citric Acid (77-92-9)
References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(i)
Log Kow: -0.28
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Calculated [X]; measured [ ]
GLP: Yes [ ] No [X] ? [ ]
Test substance: Citric Acid, Tripotassium Salt (866-84-2)
References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(j)
Log Kow: -0.28
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Calculated [X]; measured [ ]
GLP: Yes [ ] No [X] ? [ ]
Test substance: Citric Acid, Trisodium Salt (64-08-2)
References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

2.6 WATER SOLUBILITY

A. Solubility

(a)
Value: 50 g/L
Temperature: 20 °C
Description: Miscible [ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [X]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid (64-19-7)
References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(b)

Value:	1,480 g/L
Temperature:	4 °C
Description:	Miscible [ ]; Of very high solubility [X]; Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Ammonium Salt (631-61-8)
References:	Lide, D.R. (ed). 1999. CRC Handbook of Chemistry and Physics. 80th Ed. Boca Raton: CRC Press.

(c)

Value:	430 g/L
Temperature:	25 °C
Description:	Miscible [ ]; Of very high solubility [X]; Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Calcium Salt (62-54-4)
References:	Verdugt, B.V. 1992. Calcium acetate. Material Safety Data Sheet. In European Commission. 1996. Calcium Acetate. International Uniform Chemical Information Database.

(d)

Value:	Very soluble in water or alcohol
Description:	Miscible [ ]; Of very high solubility [ ]; Of high solubility [X]; Soluble [ ]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Magnesium Salt (142-72-3)
References:	Budavari, S. (ed.). 1996. Merck Index. 12th ed. Whitehouse Station: Merck Research Laboratories.

(e)

Value:	Soluble in water or alcohol
Description:	Miscible [ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [X]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Manganese Salt (638-38-0)
References:	Budavari, S. (ed.). 1996. Merck Index. 12th ed. Whitehouse Station: Merck Research Laboratories.

(f)

Value:	2,530 g/L
Description:	Miscible [X]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Potassium Salt (127-08-2)
References:	Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(g)

Value:	365 g/L
Temperature:	20 °C
Description:	Miscible [ ]; Of very high solubility [X]; Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
References:	Hoechst, A.G. 1993. Sicherheitsdatenblatt Natriumacetat entwaessert (04.03.1993). In European Commission. 1996. Sodium Acetate. International Uniform Chemical Information Database.

(h)

Value:	7 g/L
Temperature:	25 °C

Description:	Miscible [ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [X]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Fumaric Acid (110-17-8)
References:	Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(i)

Value:	592 g/L
Temperature:	25 °C
Description:	Miscible [ ]; Of very high solubility [X]; Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Malic Acid (6915-15-7)
References:	Yalkowsky, S.H. 1989. Arizona Database of Aqueous Solubilities. University of Arizona, College of Pharmacy. In Hazardous Substances Database (HSDB). Malic acid. 1999. National Library of Medicine, Bethesda, MD.

(j)

Value:	1,330 g/L
Temperature:	20 °C
Description:	Miscible [X]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)
References:	Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc

(k)

Value:	63 g/L

Description:	Miscible [ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [X]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Calculated
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Citric Acid, Tripotassium Salt (866-84-2)
References:	Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(l)

Value:	~425 g/L
Temperature:	25 °C
Description:	Miscible [ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [X]; Slightly soluble [ ] Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
References:	European Commission. 1996. Trisodium Citrate. International Uniform Chemical Information Database.

B. pH Value, pKa Value

(a)

pH Value:	2.5
Concentration:	50 g/L aqueous solution
Temperature:	20 °C
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
	(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured.)
pKa value	4.76 at 25°C
Test substance:	Acetic Acid (64-19-7)
References:	Hoescht, A.G. 1994. Produktinformation Essigsaure der Abt. Marketing Chemikalien (04.03.1994) and Sicherheitsdatenblatt Essigsaure, reinst (18.04.1994). In European Commission. 1996. Acetic Acid. International Uniform Chemical Information Database. Serjeant, E.P. and Dempsey, B. 1979. Ionisation constants of organic acids in aqueous solution. IUPAC Chem. Data Ser. No. 23. In Hazardous Substances

Database (HSDB). 1999. Acetic Acid. National Library of Medicine, Bethesda, MD.

(b)

pH Value:	7. 0
Concentration:	390 g/L (5 M aqueous solution)
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
	(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured).
Test substance:	Acetic Acid, Ammonium Salt (631-61-8)
References:	Budavari, S. (ed.). 1996. Merck Index. 12th ed. Whitehouse Station: Merck Research Laboratories.

(c)

pH Value:	7.6
Concentration:	32 g/L (0.2 M aqueous solution)
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
	(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured.)
Test substance:	Acetic Acid, Calcium Salt (62-54-4)
References:	Budavari, S. (ed.). 1996. Merck Index. 12th ed. Whitehouse Station: Merck Research Laboratories.

(d)

pH Value:	9.7
Concentration:	98 g/L (1 M aqueous solution)
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
	(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured.)
Test substance:	Acetic Acid, Potassium Salt (127-08-2)
References:	Budavari, S. (ed.). 1996. Merck Index. 12th ed. Whitehouse Station: Merck Research Laboratories.

(e)

pH Value:	7.5-9.0
Concentration:	50 g/L aqueous solution
Temperature:	20 °C

Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
	(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured.)
Test substance:	Acetic acid, sodium salt (127-09-3)
References:	Hoechst, A.G. 1993. Sicherheitsdatenblatt Natriumacetat entwaessert (04.03.1993). In European Commission. 1996. Sodium acetate. International Uniform Chemical Information Database.

(f)

pH Value:	2.1
Concentration:	5 g/L aqueous solution
Temperature:	20 °C
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
	(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured.)
pK1 value:	3.02 at 18°C
pK2:	4.46 at 18°C
Test substance:	Fumaric Acid (110-17-8)
References:	Weast, R.C. (ed.). 1989. Handbook of Chemistry and Physics. 69th Ed. Boca Raton: CRC Press. In Hazardous Substances Database (HSDB). 1999. Fumaric acid. National Library of Medicine, Bethesda, MD.

(g)

pK1 value:	3.40
pK2 value:	5.05
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Malic Acid (6915-15-7)
References:	Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. 4th Ed. Volume II, Part E: Toxicology. John Wiley & Sons, Inc.

(h)

pH Value:	2.2
Concentration:	0.1 N aqueous solution
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated

GLP:	Yes [ ] No [ ] ? [X]
	(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured.)
pK1 value:	3.13
pK2 value:	4.76
pK3 value:	6.40
Test substance:	Citric Acid (77-92-9)
References:	Budavari, S. (ed.). 1996. Merck Index. 12th ed. Whitehouse Station: Merck Research Laboratories.

(i)

pH Value:	~8
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]*
	Not stated
GLP:	Yes [ ] No [ ] ? [X]
	(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured.)
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
References:	Budavari, S. (ed.). 1996. Merck Index. 12th ed. Whitehouse Station: Merck Research Laboratories.

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

3.1.1 PHOTODEGRADATION

(a)

Type:	Air [X]; Water [ ]; Soil [ ]; Other [ ]
Light source:	Sunlight [ ]; Xenon lamp [ ]; Other [ ] Not stated
Indirect photolysis:	
Type of sensitizer:	OH
Concentration of sensitizer:	1,500,000 molecule/cm^3
Rate constant (radical):	5.1 x 10^{-13} cm^3/molecule*sec
Degradation:	~50% after 21 days
Method:	calculated [X]; measured [ ]
	[e.g. OECD, other(with the year of publication or updating of the method used)]
	Calculated by AOPWIN, Version 1.55, April 1994, Syracuse Research
GLP:	Yes [ ] No [X] ?[ ]
Test substance:	Acetic Acid (64-19-7)
Reliability:	Klimisch category 2

References:	Hoechst, A.G. 1994. Internal calculation. UCV (5.05.94). In European Commission. 1996. Acetic acid. International Uniform Chemical Information Database.

(b)

Type:	Air [ ]; Water [ ]; Soil [ ]; Other [X] Sorbed to silica gel
Light source:	Sunlight [ ]; Xenon lamp [X]; Other [ ]
Light spectrum:	290 nm
Spectrum of substance:	*[e.g. lambda (max.) (>295 nm) and epsilon (max.) or epsilon (295nm)]* >290 nm
Concentration of substance:	Not stated
Direct photolysis:	
Degradation:	6.6 % of applied amount after 17 hour exposure
Method:	calculated [ ]; measured [X] *[e.g. OECD, other(with the year of publication or updating of the method used)]* The test material was sorbed on silica gel and irradiated with light at 290 nm.
GLP:	Yes [ ] No [X] ?[ ]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Reliability:	Klimisch category 2
References:	Freitag, D., Ballhorn, L. Geyer, H., and Korte, F. 1985. Environmental hazard profile of organic chemicals: An experimental method for the assessment of he behavior of organic chemicals in the ecosphere by means of simple laboratory tests with C14 labeled chemicals. Chemosphere 14(10):1589-1616.

(c)

Type:	Air [X]; Water [ ]; Soil [ ]; Other [ ]
Light source:	Sunlight [ ]; Xenon lamp [ ]; Other [ ] Not stated
Relative intensity:	Not stated
Indirect photolysis:	
Type of sensitizer:	OH
Concentration of sensitizer:	500,000 molecule/cm^3
Rate constant (radical):	5.3 x 10^{-12} cm^3/molecule*sec
Degradation:	50% after 7.3 hours
Method:	calculated [X]; measured [ ] *[e.g. OECD, other(with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [X] ?[ ]
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 2
References:	Atkinson, R. 1987. A structure-activity relationship for the estimation of rate constants for the gas-phase reactions of OH radicals with organic compounds. J. Inter. Chem. Kinet. 19:799-828.

(d)

Type:	Air [X]; Water [ ]; Soil [ ]; Other [ ]
Indirect photolysis:	
Type of sensitizer:	OH
Concentration of sensitizer:	5 x 10^5 molecules/cm^3
Rate constant (radical):	7.76 x 10^{-12} cm^3/molecule*sec
Degradation:	Malic acid will degrade in the vapor phase by reaction with photochemically produced hydroxyl radicals at the stated rate, which corresponds to an atmospheric half-life of about 2 days.
Method:	*[e.g. OECD, other(with the year of publication or updating of the method used)]*
GLP:	Yes [ ] No [ ] ?[X]
Test substance:	Malic Acid (6915-15-7)
Reliability:	Klimisch category 2
References:	Meylan, W.M. and Howard, P.H. 1993. Chemosphere 26:2293-2299. In Hazardous Substances Database (HSDB). 1999. Malic acid. National Library of Medicine, Bethesda, MD.

3.1.2 STABILITY IN WATER

(a)

Remarks:	Acids dissociate in water.
Test substance:	Acetic Acid (64-19-7)

(b)

Remarks:	Salts dissociate in water.
Test substance:	Acetic Acid, Ammonium Salt (631-61-8)

(c)

Remarks:	Salts dissociate in water.
Test substance:	Acetic acid, calcium salt (62-54-4)

(d)

Remarks:	Salts dissociate in water.
Test substance:	Acetic acid, potassium salt (127-08-2)

(e)

Remarks:	Salts dissociate in water.
Test substance:	Acetic acid, sodium salt (127-09-3)

(f)

Type:	Abiotic (hydrolysis) [ ]; biotic (sediment) [ ]
Half life:	1-15 days in various natural waters
Method:	*[e.g. OECD, other(with the year of publication or updating of the method used)]* River die-away studies
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Fumaric Acid (110-17-8)

Remarks:	*(e.g. CAS number, name and percentage of degradation products)* Faster degradation occurred in more polluted waters. The degradation half life in distilled water was 55 days.
Reliability:	Klimisch category 2
References:	Saito, N. and Nagao, M. 1978. Okayama-Ken Kankyo Hoken Senta Nempo 2:274-276. In Hazardous Substances Database (HSDB). Fumaric acid. 1999. National Library of Medicine, Bethesda, MD.

(g)

Remarks:	When released into natural water, malic acid can be expected to biodegrade readily; as shown by a number of screening tests.
Test substance:	Malic Acid (6915-15-7)
Reliability:	Klimisch category 2
References:	Fournier, J.C, Hormatallah, A., Collu, T., and Froncek, B. 1992. Labelling of microbial biomass with radioactive substrates as a means to estimate pesticide effects in soil. Sci. Total Environ. 123/124:325-332.

(h)

Remarks:	Acids dissociate in water.
Test substance:	Citric Acid (77-92-9)

(i)

Remarks:	Salts dissociate in water.
Test substance:	Citric Acid, Sodium Salt (994-36-5)

(j)

Remarks:	Salts dissociate in water.
Test substance:	Citric Acid, Tripotassium Salt (866-84-2)

(k)

Remarks:	Salts dissociate in water.
Test substance:	Citric Acid, Trisodium Salt (64-08-2)

(l)

Remarks:	Salts dissociate in water.
Test substance:	Acetic acid, manganese salt (638-38-0)

(m)

Remarks:	Salts dissociate in water.
Test substance:	Acetic Acid, Magnesium Salt (142-72-3)

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

Type:	Level I Fugacity Modeling
Temperature:	25 °C
Melting Point:	16.7 °C
Vapor Pressure:	1520 Pa (11.4 mm Hg)
Water Solubility:	50,000 g/m^3 (50 g/L)
Octanol-Water Partition:	0.676
Reaction Half-Lives:	Air: 21 days
	Water: 1 day
	Soil: 1 day
	Sediment: 1 day
Results:	Partitioning to:
	Air: 26.9 %
	Water: 73.1%
	Soil: 0.044%
	Sediment: 9.72 x 10^{-4} %
	Suspended Sediment: 3.04 x 10^{-5} %
	Fish: 2.47 x 10^{-6} %
Test Substance:	Acetic Acid (64-17-9)
Reliability:	Klimisch category 2
Reference:	Mackay 1991

Type:	Level I Fugacity Modeling
Temperature:	25 °C
Melting Point:	287 °C
Vapor Pressure:	0.0205 Pa (1.54 x 10^{-4} mm Hg)
Water Solubility:	7,000 g/m^3 (7 g/L)
Octanol-Water Partition:	2.138
Reaction Half-Lives:	Air: 0.3 days
	Water: 1 day
	Soil: 1 day
	Sediment: 1 day
Results:	Partitioning to:
	Air: 6.84 x 10^{-3} %
	Water: 99.8%
	Soil: 0.189%
	Sediment: 4.20 x 10^{-3} %
	Suspended Sediment: 1.31 x 10^{-4} %
	Fish: 1.07 x 10^{-5} %
Test Substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 2
Reference:	Mackay 1991

Type:	Level I Fugacity Modeling
Temperature:	25 °C
Melting Point:	128 °C
Vapor Pressure:	6.1 x 10^{-4} Pa (4.6 x 10^{-6} mm Hg)
Water Solubility:	592,000 g/m^3 (592 g/L)
Octanol-Water Partition:	0.055
Reaction Half-Lives:	Air: 2 days
	Water: 1 day
	Soil: 1 day
	Sediment: 1 day
Results:	Partitioning to:
	Air: 2.79 x 10^{-6} %
	Water: 100.0%
	Soil: 4.87 x 10^{-3} %
	Sediment: 1.08 x 10^{-4} %
	Suspended Sediment: 3.38 x 10^{-6} %
	Fish: 2.75 x 10^{-7} %
Test Substance:	Malic Acid (6915-15-7)
Reliability:	Klimisch category 2
Reference:	Mackay 1991

Type:	Level I Fugacity Modeling
Temperature:	25 °C
Melting Point:	153 °C
Vapor Pressure:	4.9 x 10^{-7} Pa (3.7 x 10^{-9} mm Hg)
Water Solubility:	1.33 x 10^6 g/m^3 (1330 g/L)
Octanol-Water Partition:	0.019
Reaction Half-Lives:	Water: 1 day
	Soil: 1 day
	Sediment: 1 day
Results:	Partitioning to:
	Air: 1.43 x 10^{-9} %
	Water: 100.0%
	Soil: 1.69 x 10^{-3} %
	Sediment: 3.75 x 10^{-5} %
	Suspended Sediment: 1.17 x 10^{-6} %
	Fish: 9.53 x 10^{-8} %
Test Substance:	Citric Acid (77-92-9)
Reliability:	Klimisch category 2
Reference:	Mackay 1991

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

Remarks: See biodegradation

3.5 BIODEGRADATION

(a)

Type:	Aerobic [ ]; Anaerobic [X]
Inoculum:	Adapted [ ]; Non-adapted [X];
Concentration of the chemical:	30 mg-C/l related to COD [ ]; DOC [X]; Test substance [ ]
Medium:	Water [ ]; Water-sediment [ ]; Soil [ ]; Sewage treatment [X]
Degradation:	99 % reduction after 7 days
Results:	Readily biodeg. [X]; Inherently biodeg. [ ]; Under test condition no biodegradation observed [ ]; Other [ ]
Method:	*[e.g. OECD, others(with the year of publication or updating of the method used)]* Test procedures were carried out in an enclosed glove box with N_2 atmosphere. Oxygen-free water was used. The test period was 4 weeks at 37 °C and with pH adjusted to 7. Biodegradation was determined by analyzing the decrease of DOC.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic acid (64-17-9)
Reliability:	Klimisch category 2
References:	Kameya, T., Murayama, T., Urano, K., and Kitano, M. 1995. Biodegradation ranks of priority organic compounds under anaerobic conditions. Sci. Total Environ. 170(1-2):43-51.

(b)

Results:	Biodegrades in days to weeks.
Method:	*[e.g. OECD, others(with the year of publication or updating of the method used)]* Calculated.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Ammonium Salt (631-61-8)
Reliability:	Klimisch category 2
References:	Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(c)

Type:	Aerobic [X]; Anaerobic [ ]
Medium:	Water [ ]; Water-sediment [ ]; Soil [ ]; Sewage treatment [X]
Results:	Readily biodeg. [X]; Inherently biodeg. [ ]; Under test condition no biodegradation observed [ ]; Other [ ]
Method:	*[e.g. OECD, others(with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic acid, calcium salt (62-54-4)

Remarks:	Activated sludge, industrial
Reliability:	Klimisch category 4
References:	European Commission. 1996. Calcium acetate. International Uniform Chemical Information Database.

(d)

Type:	Aerobic [X]; Anaerobic [ ]
Inoculum:	Adapted [ ]; Non-adapted [X]; activated sludge
Concentration of the chemical:	160 mg/L related to COD [ ]; DOC [ ]; Test substance [X]
Medium:	Water [ ]; Water-sediment [ ]; Soil [ ]; Sewage treatment [X]
Degradation:	100 % reduction after 5 days
Results:	Readily biodeg. [ ]; Inherently biodeg. [X]; Under test condition no biodegradation observed [ ]; Other [ ]
Method:	*[e.g. OECD, others(with the year of publication or updating of the method used)]* OECD Guideline 302B (1981) "Inherent biodegradability: Modified Zahn-Wellens Test"
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Reliability:	Klimisch category 2
References:	Huels study (unpublished). In European Commission. 1996. Sodium acetate. International Uniform Chemical Information Database.

(e)

Type:	Aerobic [X]; Anaerobic [ ]
Inoculum:	Adapted [ ]; Non-adapted [X];
Concentration of the chemical:	0.05 mg/L related to COD [ ]; DOC [ ]; Test substance [X]
Medium:	Water [ ]; Water-sediment [ ]; Soil [ ]; Sewage treatment [X]
Degradation:	52.6 % reduction after 5 days
Results:	Readily biodeg. [ ]; Inherently biodeg. [X]; Under test condition no biodegradation observed [ ]; Other [ ]
Method:	*[e.g. OECD, others(with the year of publication or updating of the method used)]* Batch-Test; mineralization related to maximum theoretical CO_2-production; measurement of 14 CO_2; Temperature was maintained at 25 ± 2 °C.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Reliability:	Klimisch category 2
References:	Freitag, D., Ballhorn, L., Geyer, H., and Korte, F. 1985. Environmental hazard profile of organic chemicals: An experimental method for the assessment of he behavior of organic chemicals in the ecosphere by means of simple laboratory tests with C14 labeled chemicals. Chemosphere 14(10):1589-1616.

(f)

Type:	Aerobic [X]; Anaerobic [ ]
Inoculum:	Adapted [ ]; Non-adapted [X]; predominantly domestic sewage
Concentration of the chemical:	10 mg/L related to COD [ ]; DOC [X]; Test substance [ ]
Medium:	Water [ ]; Water-sediment [ ]; Soil [ ]; Sewage treatment [X]
Degradation:	98 % reduction after 21 days
Results:	Readily biodeg. [X]; Inherently biodeg. [ ]; Under test condition no biodegradation observed [ ]; Other [ ]
Method:	*[e.g. OECD, others(with the year of publication or updating of the method used)]* OECD Guideline 301 E (1981) "Ready biodegradability: Modified OECD Screening Test"
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 2
References:	Huels, A.G. 1992. Unpublished results dated 3/4/92. In European Commission. 1996. Fumaric acid. International Uniform Chemical Information Database.

(g)

Type:	Aerobic [X]; Anaerobic [ ]
Inoculum:	Adapted [ ]; Non-adapted [X]; domestic sewage
Concentration of the chemical:	600 mg/L related to COD [ ]; DOC [ ]; Test substance [X]
Medium:	Water [ ]; Water-sediment [ ]; Soil [ ]; Sewage treatment [X]
Degradation:	98 % reduction after 48 hours
Results:	Readily biodeg. [X]; Inherently biodeg. [ ]; Under test condition no biodegradation observed [ ]; Other [ ]
Kinetics:	0% in 0 hours 34% in 18 hours 84% in 24 hours 97% in 40 hours 98% in 48 hours
Method:	*[e.g. OECD, others(with the year of publication or updating of the method used)]* OECD Guideline 302 B (1994)"Inherent biodegradability: Modified Zahn-Wellens Test"
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Citric Acid (77-92-9)
Reliability:	Klimisch category 2
References:	European Commission. 1996. Citric acid. International Uniform Chemical Information Database.

(h)

Type:	Aerobic [X]; Anaerobic [ ]
Inoculum:	Adapted [ ]; Non-adapted [ ]; effluent from domestic sewage treatment plant

Concentration of the chemical:	5 mg/L related to COD [ ]; DOC [ ]; Test substance [X]
Medium:	Water [ ]; Water-sediment [ ]; Soil [ ]; Sewage treatment [X]
Degradation:	90 % reduction after 30 days
Results:	Readily biodeg. [X]; Inherently biodeg. [ ]; Under test condition no biodegradation observed [ ]; Other [ ]
Method:	*[e.g. OECD, others(with the year of publication or updating of the method used)]*
GLP:	Yes [ ] No [X] ? [ ] Directive 84/449/EEC, C.6 "Biotic degradation – closed bottle test"
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
Reliability:	Klimisch category 2
References:	European Commission. 1996. Trisodium citrate. International Uniform Chemical Information Database.

3.7 BIOACCUMULATION

Remarks:	Does not bioaccumulate because these acids and their salts dissociate and biodegrade rapidly.

4. ECOTOXICITY

4.1 ACUTE/PROLONGED TOXICITY TO FISH

(a)

Type of test:	Static [ ]; Semi-static [ ]; Flow-through [ ]; Other *(e.g. field test)* [ ]; Not stated
Species:	*Lepomis macrochirus* (Bluegill sunfish)
Exposure period:	96 hours
Results:	LC_{50} (96 h) = 75 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
Remarks:	Data from unknown literature source as cited by Price.
Reliability:	Klimisch category 2
References:	Price, K.S., Waggy, G.T., and Conway, R.A. 1974. Brine shrimp bioassay and seawater BOD of petrochemicals. J. Water Pollut Control Fed. 46(1):63-77.

(b)

Type of test:	Static [X]; Semi-static [ ]; Flow-through [ ]; Other *(e.g. field test)* [ ]; Not stated
Species:	*Gambusia affinis* (Mosquito fish)
Exposure period:	96 hours
Results:	LC_{50} (96 h) = 251 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Test water was maintained at pH 6.9 – 8.7 and 16-25°C
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
Remarks:	Test data from original citation.
Reliability:	Klimisch category 2
References:	Wallen I.E., Greer, W.C., and Lasater, R. 1957. Toxicity to *Gambusia affinis* of certain pure chemicals in turbid waters. Sewage Ind. Wastes 23(6):695-711.

(c)

Type of test:	Static [X]; Semi-static [ ]; Flow-through [ ]; Other *(e.g. field test)* [ ]; Not stated
Species:	*Pimephales promelas* (Fathead minnow)
Exposure period:	96 hours
Results:	LC_{50} (96 h) = 79-88 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Fathead minnows were exposed under static conditions to a series of concentrations of ammonium acetate.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Ammonium Salt (631-61-8)
Reliability:	Klimisch category 2
References:	Mattson, V.R., Arthur, J.W., and Walbridge, C.A. 1976. Acute toxicity of selected organic compounds to fathead minnows. Ecol. Res. Ser. EPA-600/3-76-097, Environ. Res. Lab., USEPA, Duluth, MN: 12p.

(d)

Type of test:	Static [ ]; Semi-static [ ]; Flow-through [ ]; Other *(e.g. field test)* [ ]; Not stated
Species:	*Gambusia affinis* (Mosquito fish)
Exposure period:	96 hours
Results:	LC_{50} (96 h) = 238 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Ammonium Salt (631-61-8)
Reliability:	Klimisch category 4

References:	Jones, H.R. 1971. Environmental control in the organic and petrochemical industries. Noyes Data Corporation. In Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(e)

Type of test:	Static [ ]; Semi-static [X]; Flow-through [ ]; Other *(e.g. field test)* [ ]
Species:	*Salmo gairdneri* (Rainbow trout)
Exposure period:	96 hours
Results:	LC_{50} (96 h) = 6,100 mg/L
Analytical monitoring:	Yes [ ]; No [X]; ? [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* OECD Guideline 203
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic acid, potassium salt (127-08-2)
Remarks:	Test used a commercial formulation.
Reliability:	Klimisch category 2
References:	Huntingdon Research Centre. 1992. Report No. BPC142/911702. In European Commission. 1996. Potassium acetate. International Uniform Chemical Information Database.

(f)

Type of test:	Static [ ]; Semi-static [X]; Flow-through [ ]; Other *(e.g. field test)* [ ]
Species:	*Brachydanio rerio* (Zebra fish)
Exposure period:	96 hours
Results:	LC_{50} (96 h) >100 mg/L
Analytical monitoring:	Yes [X]; No [ ]; ? [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Directive 92/69/EEC, C.1 (1992)
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Remarks:	Concentration refers to waterfree substance. No mortality was observed at the highest concentration tested.
Reliability:	Klimisch category 2
References:	Huels. 1993. Report No. FK 1241 (unpublished). In European Commission. 1996. Sodium acetate. International Uniform Chemical Information Database.

(g)

Type of test:	Static [X]; Semi-static [ ]; Flow-through [ ]; Other *(e.g. field test)* [ ]
Species:	*Pimephales promelas* (Fathead minnow)
Exposure period:	120 hours
Results:	LC_{50} (96 h) = 13.3 mg/L

Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Fathead minnow embryos were exposed to increasing concentrations of acetic acid sodium salt for 5 days under static conditions.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Remarks:	95% confidence intervals were 12.43 and 14.31 mg/L.
Reliability:	Klimisch category 2
References:	DeYoung, D.J., Bantle, J.A., Hull, M.A., and Burks, S.L. 1996. Differences in sensitivity to developmental toxicants as seen in *Xenopus* and *Pimephales* embryos. Bull. Environ. Contam. Toxicol. 56:143-150.

(h)

Type of test:	Static [X]; Semi-static [ ]; Flow-through [ ]; Other *(e.g. field test)* [ ]
Species:	*Brachydanio rerio* (Zebra fish)
Exposure period:	48 hours
Results:	LC_{50} (48 h) = 245 mg/L
Analytical monitoring:	Yes [ ]; No [X]; ? [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* DIN 38412 Part 15
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 2
References:	Huels Ag: AIDA – Grunddatensatz, date of last update 0.4.03.92. In European Commission. 1996. Fumaric acid. International Uniform Chemical Information Database.

(i)

Type of test:	Static [X]; Semi-static [ ]; Flow-through [ ]; Other *(e.g. field test)* [ ]
Species:	*Lepomis macrochirus* (Bluegill sunfish)
Exposure period:	96 hours
Results:	LC_{50} (96 h) = 1,516 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)
Reliability:	Klimisch category 4
References:	Schwartz and Davis. 1973. United States Environmental Protection Agency (USEPA). EPA-600/2-74-003. In European Commission. 1996. Citric acid. International Uniform Chemical Information Database.

(j)

Type of test:	Static [ ]; Semi-static [ ]; Flow-through [ ]; Other *(e.g. field test)* [ ]; Not stated
Species:	*Poecilia reticulata* (Guppy)
Exposure period:	96 hours
Results:	LC_{50} (96 h) >18,000-32,000 mg/L
Analytical monitoring:	Yes [X]; No [ ]; ? [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
Remarks:	The same result was obtained in a study on *Oryzias latipes* (medaka).
Reliability:	Klimisch category 4
References:	Sloof, W. and Kappers, F.I. 1982. Rijksinstituut voor drinkwatervoorziening (RID) Nr. 82-4. In European Commission. 1996. Trisodium citrate. International Uniform Chemical Information Database.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

A. *Daphnia*

(a)

Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other *(e.g. field test)* [ ];
Species:	*Daphnia magna*
Exposure period:	24 hours
Results:	LC_{50} = 47 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
Remarks:	Based on the results reported in Bringmann and Kuhn 1982 (see next summary for reference), this value is likely attributed to the low pH of the system.
Reliability:	Klimisch category 2

References:	Elkins, H.F., et al. 1956. Sewage Ind. Wastes 28(12): 1475. In Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(b)

Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other [ ]
Species:	*Daphnia magna*
Exposure period:	24 hours
Results:	EC_{50} = 6,000 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* The stock cultures of test organisms were fed dry algae, but no feeding occurred during the 24-hour exposure. The testing took place in a defined standardized culture medium (artificial fresh water). The endpoint was immobilization.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
Remarks:	The stated result was for test solutions neutralized (pH 8.0) prior to daphnid exposures. For the un-neutralized test, the 24-hour EC_{50} was 95 mg/L. The pH of un-neutralized test solutions was not stated.
Reliability:	Klimisch category 2
References:	Bringmann, V. G. and Kuhn, R. 1982. Results of toxic action of water pollutants on *Daphnia magna strauss* tested by an improved standardized procedure. Z. Wasser Abwasser Forsch. 15(1):1-6.

(c)

Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other [ ]
Species:	*Daphnia magna*
Exposure period:	48 hours
Results:	EC_{50} = 65 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* *Daphnia magna* were exposed to a series of concentrations of acetic acid. The endpoint was immobilization.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
Remarks:	Test solutions were apparently un-neutralized.
Reliability:	Klimisch category 2
References:	Janssen, C.R., Espiritu, E.Q., and Persoone, G. 1993. Evaluation of the new "Enzymatic Inhibition" criterion for rapid toxicity testing with *Daphnia magna*. In: Soares, A. and Calow, P. (Eds.), Progress in Standardization of Aquatic Toxicity Tests. Lewis Publishers, New York, pp. 71-81.

(d)

Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other *(e.g. field test)* [ ]; Not stated
Species:	*Daphnia magna*
Exposure period:	24 hours
Results:	LC_{50} = 7,170 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Remarks:	Was summarized in the Potassium acetate IUCLID Data Sheet but indicated the test substance was acetic acid, sodium salt.
Reliability:	Klimisch category 4
References:	Bringmann and Kuhn. 1977. Z. Wasser Abwasser Forschung 10(5):161-166. In European Commission. 1996. Potassium acetate. International Uniform Chemical Information Database.

(e)

Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other *(e.g. field test)* [ ]; Not stated
Species:	*Daphnia magna*
Exposure period:	48 hours
Results:	EC_{50} > 1,000 mg/L
Analytical monitoring:	Yes [ ]; No [X]; ? [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Directive 84/449/EEC, C.2
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Reliability:	Klimisch category 2
References:	Huels. 1993. Report No. FK 1241 (unpublished). In European Commission. 1996. Sodium acetate. International Uniform Chemical Information Database.

(f)

Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other *(e.g. field test)* [ ]
Species:	*Daphnia magna*
Exposure period:	48 hours EC_{50} = 212 mg/L
Analytical monitoring:	Yes [ ]; No [X]; ? [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* First instar *Daphnia* (< 24 hrs old) were used for all tests. Method as described in EPA-660/3-75-009.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Fumaric Acid (110-17-8)

Remarks:	Endpoint was immobilization.
Reliability:	Klimisch category 2
References:	Randall, T.L. and Knopp, P.V. 1980. Detoxification of specific organic substances by wet oxidation. J. Water Pollut. Control Fed. 52(8):2117-2130. United States Environmental Protection Agency (USEPA). 1975. Methods for acute toxicity tests with fish, macroinvertebrates, and amphibians. Ecological Research Series, EPA-660/3-75-009.

(g)

Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other *(e.g. field test)* [ ]
Species:	*Daphnia magna*
Exposure period:	48 hours
Results:	LC_{50} = 240 mg/L
Analytical monitoring:	Yes [ ]; No [X]; ? [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Fifteen daphnids (≤24-hours old, first instar) were exposed to concentrations of 100, 180, 320, 560 and 1,000 mg/L, along with a control group. Test temperature remained constant at 20 °C throughout the study.
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Malic Acid (6915-15-7)
Remarks:	Mortality and/or surfacing was observed in test concentrations ≥180 mg/L. Low pH (3.2-4.5) caused by the acidic test material may be considered the primary cause of the observed toxicity.
Reliability:	Klimisch category 1
References:	ABC Laboratories. 1989. Acute freshwater invertebrate toxicity study – malic acid. Report # 37763. Prepared for Proctor & Gamble.

(h)

Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other *(e.g. field test)* [ ]; Not stated
Species:	*Daphnia magna*
Exposure period:	24 hours
Results:	EC_{50} = 1,535 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* The stock cultures of test organisms were fed dry algae, but no feeding occurred during the 24-hour exposure. The testing took place in a defined standardized culture medium (artificial fresh water). The endpoint was immobilization.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)

Reliability:	Klimisch category 2
References:	Bringmann, V. G. and Kuhn, R. 1982. Results of toxic action of water pollutants on *Daphnia magna strauss* tested by an improved standardized procedure. Z. Wasser Abwasser Forsch. 15(1):1-6.

(i)

Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other *(e.g. field test)* [ ]; Not stated
Species:	*Daphnia magna*
Exposure period:	72 hours
Results:	EC_{50} = 120 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)
Reliability:	Klimisch category 4
References:	Ellis, M.M. 1937. Bull. Bur. Fish 48:365. In European Commission. 1996. Citric acid. International Uniform Chemical Information Database.

(j)

Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other *(e.g. field test)* [ ]; Not stated
Species:	*Daphnia magna*
Exposure period:	48 hours
Results:	EC_{50} = 5,600 – 10,000 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Trisodium Salt (64-08-2), purity: 50%
Reliability:	Klimisch category 4
References:	Sloof, W. and Kappers, F.I. 1982. Rijksinstituut voor drinkwatervoorziening (RID) Nr. 82-4. In European Commission. 1996. Trisodium citrate. International Uniform Chemical Information Database.

4.3 TOXICITY TO AQUATIC PLANTS, e.g. algae

(a)

Species:	*Scenedesmus quadricauda* (algae)
Endpoint:	Biomass [ ]; Growth rate [ ]; Other [X](Growth inhibition)
Exposure period:	8 days
Results:	TT (toxicity threshold) = 4,000 mg/L

Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Filled culture tubes were maintained at 27 °C and relative humidity of 50%. The concentration of the algal suspension is measured turbidmetrically (while diffused light is screened off) and expressed by the extinction of the primary light of the monochromatic radiation at 578 nm for a layer of 10 mm thickness.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid (64-19-7)
Remarks:	Toxicity threshold is defined as the pollutant concentration resulting in a mean extinction value that is ≥ 3% below the mean of the extinction value for the non-toxic dilutions of the test culture.
Reliability:	Klimisch category 2
References:	Bringmann, G. and Kuhn, R. 1980. Comparison of the toxicity thresholds of water pollutants to bacteria, algae, and protozoa in the cell multiplication inhibition test. Water Res. 14:231-241.

(b)

Species:	*Anacystis nidulans* (Cyanobacterium)
Endpoint:	Biomass [ ]; Growth rate [X]; Other [ ]
Exposure period:	60 hours
Results:	Growth inhibition in photoautotrophic algae at 2,460 mg/L (0.03 mol/L) after 60 hours.
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* A static test was conducted at a temperature of 30°C, a pH of 7.6-7.8, and a light intensity of 1,000 ft. candles. Growth rate was determined by measuring optical density of the cultures.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Remarks:	Retardation of growth (i.e., slowed but did not otherwise restrict growth) occurred at 820 and 1,640 mg/L (0.01 and 0.02 mol/L). Inhibition of growth (i.e., prevented growth) occurred at 2,460 and 3,290 mg/L (0.03 and 0.04 mol/L). However, even at the highest concentrations, the cultures remained viable after being transferred to clean culture water.
Reliability:	Klimisch category 2
References:	Hoare, D.S. et al. 1967. J. Gen. Microbiol. 49:351-370. In European Commission. 1996. Sodium Acetate. International Uniform Chemical Information Database.

(c)

Species:	*Scenedesmus subspicatus* (Algae)
Endpoint:	Biomass [ ]; Growth rate [X]; Other [ ]

Exposure period:	72 hours
Results:	EC_{10} (72 h) = 32 mg/L EC_{50} (72 h) = 41 mg/L CE_{90} (72 h) = 49 mg/L
Analytical monitoring:	Yes [ ]; No [X]; ? [ ]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* UBA algal growth inhibition test (proposed method February 1984)
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 2
References:	AIDA – Huels AG Report No. AW 1501. 1988. Not published. In European Commission. 1996. Fumaric Acid. International Uniform Chemical Information Database.

(d)

Species:	*Scenedesmus quadricauda* (algae)
Endpoint:	Biomass [ ]; Growth rate [ ]; Other [X](Growth inhibition)
Exposure period:	8 days
Results:	TT (toxicity threshold) = 640 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* Filled culture tubes were maintained at 27 °C and relative humidity of 50%. The concentration of the algal suspension is measured turbidmetrically (while diffused light is screened off) and expressed by the extinction of the primary light of the monochromatic radiation at 578 nm for a layer of 10 mm thickness.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Citric Acid (77-92-9)
Remarks:	Toxicity threshold is defined as the pollutant concentration resulting in a mean extinction value that is ≥ 3% below the mean of the extinction value for the non-toxic dilutions of the test culture.
Reliability:	Klimisch category 2
References:	Bringmann, G. and Kuhn, R. 1980. Comparison of the toxicity thresholds of water pollutants to bacteria, algae, and protozoa in the cell multiplication inhibition test. Water Res. 14:231-241.

(e)

Species:	*Chlorella vulgaris*
Endpoint:	Biomass [X]; Growth rate [ ]; Other [ ]
Exposure period:	96 hours
Results:	EC_{50} > 18,000 – 32,000 mg/L
Analytical monitoring:	Yes [X]; No [ ]; ? [ ]

Method:	*[e.g. OECD, other (with the year of publication or updated of the method used)]* OECD Guideline 201 (1982) "Algae, Growth Inhibition Test"
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Trisodium Salt (64-08-2); purity: 50% solution
Reliability:	Klimisch category 2
References:	Sloof, W. and Kappers, F.I. 1982. Rijksinstituut voor drinkwatervoorziening (RID) Nr. 82-4. In European Commission. 1996. Trisodium citrate. International Uniform Chemical Information Database.

5. TOXICITY

5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

(a)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mouse
Value:	4960 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
Reliability:	Klimisch category 4
References:	Woodward, G., Lang, S.R., Nelson, K.W., and Calvery, H.O. 1941. J. Ind. Hyg. Toxicol. 23:78-82. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. Volume II, Part E. Toxicology. New York: John Wiley & Sons, Inc.

(b)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Value:	4,280 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Rats were given a single oral dose of 200,000 mg/L (0.200 g/ml) of acetic acid, calcium salt in water via intubation. A range-finding toxicity test was conducted as described in Smyth et al. 1962.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Calcium Salt (62-54-4)
Reliability:	Klimisch category 2

References: Smyth, H.F., Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C., Striegel, J.A., and Nycum, J.S. 1969. Range-finding toxicity data: List VII. Am. Ind. Hyg. Assoc. J. 30:470-476.
Smyth, H.F. Jr., Carpenter, C.P., Weil, C.S., Pozzani,, U.C., and Striegel, J.A. 1962. Range-finding toxicity data: List VI. Amer. Ind. Hyg. Assoc. J. 23:95-207.

(c)
Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Rat
Value: 3,250 mg/kg b.w.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Rats were given a single oral dose of 100,000 mg/L (0.100 g/ml) of acetic acid, potassium salt in water via intubation. A range-finding toxicity test was conducted as described in Smyth et al. 1962.
GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid, Potassium Salt (127-08-2)
Reliability: Klimisch category 2
References: Smyth, H.F., Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C., Striegel, J.A., and Nycum, J.S. 1969. Range-finding toxicity data: List VII. Am. Ind. Hyg. Assoc. J. 30:470-476.
Smyth, H.F. Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C., and Striegel, J.A. 1962. Range-finding toxicity data: List VI. Amer. Ind. Hyg. Assoc. J. 23:95-207.

(d)
Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Rat
Value: 3,530 mg/kg b.w.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid, Sodium Salt (127-09-3)
Reliability: Klimisch category 2
References: Food and Agriculture Organization of the United Nations, Report Series. 40,127,67. In Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(e)
Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Rat
Value: 10,700 mg/kg b.w. (male rats)
9,300 mg/kg b.w. (female rats)

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Rats were given a single oral dose. Range finding toxicity test as described in Smyth et al. 1962.
GLP: Yes [ ] No [ ] ? [X]
Test substance: Fumaric Acid (110-17-8)
Reliability: Klimisch category 2
References: Vernot, E.H., MacEwen, J.D., Haun, C.C., and Kinkead, E.R. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42:417-423.
Smyth, H.F. Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C., and Striegel, J.A. 1962. A range-finding toxicity data: List VI. Amer. Ind. Hyg. Assoc. J. 23:95-207.

(f)
Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Rat
Value: 10,000 mg/kg b.w.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Fumaric Acid (110-17-8)
Reliability: Klimisch category 4
References: Ullmann's Encyclopedia of Industrial Chemistry. 5^{th} Ed. Volume A16. In European Commission. 1996. Fumaric acid. International Uniform Chemical Information Database.

(g)
Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Mouse, Rat
Value: 1,600 – 3,200 mg/kg b.w.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Malic Acid (6915-15-7)
Reliability: Klimisch category 2
References: Eastman Kodak. 1981. Health Safety and Human Factors Laboratory, Rochester, New York. In BIBRA. 1992. Toxicology profile: Malic acid and its common salts. BIBRA International.

(h)
Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Rat (Sprague-Dawley)
Value: 11,700 mg/kg b.w.

Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Six 5-week old male SD-JCL rats weighing 110-140 g were used at each dosage group. A single oral dose was administered for each of a series of concentrations in volumes of 2 ml/100 g body weight. Behavior and mortality were observed for 7 days.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Citric Acid (77-92-9), purity: 99.8% citric acid monohydrate
Remarks:	Observed effects at the higher concentration included motor ataxia, decreases in respiration and heart beat, and respiratory failure.
Reliability:	Klimisch category 2
References:	Yokotani, H., Usui, T., Nakaguchi, T., Kanabayashi, T. Tanda, M., and Aramaki, Y. 1971. Acute and subacute toxicological studies of TAKEDA-citric acid in mice and rats. J. Takeda Res. Lab. 30(1):25-31.

(i)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mouse (1 CR)
Value:	5,790 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Six 4-week old male ICR-JCL mice weighing 20-24 g were used at each dosage group. A single oral dose was administered for each of a series of concentrations in volumes of 0.5 ml/10 g b.w. Behavior and mortality were observed for 7 days.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Citric Acid (77-92-9), purity : 99.8% citric acid monohydrate
Remarks:	Observed effects at the higher concentration included motor ataxia, decreases in respiration and heart beat, and respiratory failure.
Reliability:	Klimisch category 2
References:	Yokotani, H., Usui, T., Nakaguchi, T., Kanabayashi, T. Tanda, M., and Aramaki, Y. 1971. Acute and subacute toxicological studies of TAKEDA-citric acid in mice and rats. J. Takeda Res. Lab. 30(1):25-31.

(j)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mouse
Value:	7,100 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Sodium Salt (994-36-5)

Reliability:	Klimisch category 4
References:	Oelkers, H.A. 1965. Theor. Med. 19:625. In BIBRA. 1993. Toxicology Profile: Citric acid and its common salts. BIBRA International.

(k)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat (Wistar)
Value:	8,610 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* A group of 30 albino male and female rats (five per dose) were given either 1.0, 2.0, 4.0, 8.0, 16.0 or 32.0 g/kg bw of acetic acid, magnesium salt in propylene glycol via intubation.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Magnesium Salt (142-72-3)
Remarks:	No toxic effects were noted at the 1.0 and 2.0 g/kg doses. Diarrhea and ruffled unkempt coats were evident 24-36 hours after intubation at the 4.0 g/kg dose. Deaths in the 16.0 and 32.0 g/kg doses occurred 8-16 hours and within 6 hours, respectively.
Reliability:	Klimisch category 2
References:	Green, L.A. 1977. Toxicity Studies for The Shepherd Chemical Company: Acute Oral LD_{50} Toxicity Study: Magnesium Acetate. Bio-Toxicology Laboratories, May 31, 1977.

(l)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Value:	3,730 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Rats were given a single oral dose of 200,000 mg/L (0.200 g/ml) of acetic acid, manganese salt in water via intubation. A range-finding toxicity test was conducted as described in Smyth et al. 1962.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Manganese Salt (638-38-0)
Reliability:	Klimisch category 2
References:	Smyth, H.F., Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C., Striegel, J.A., and Nycum, J.S. 1969. Range-finding toxicity data: List VII. Am. Ind. Hyg. Assoc. J. 30:470-476. Smyth, H.F. Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C., and Striegel, J.A. 1962. Range-finding toxicity data: List VI. Amer. Ind. Hyg. Assoc. J. 23:95-207.

5.1.2 ACUTE INHALATION TOXICITY

(a)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [X]; LCL_0 [ ]; Other [ ]
Species/strain:	Rat
Exposure period:	4 hours
Value:	11.4 mg/l
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* BASF-Test Protocol
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid (64-19-7); purity: 96%
Reliability:	Klimisch category 2
References:	BASF, A.G. 1989. Unpublished study No. 78/650, 21.05.1980. In European Commission. 1996. Acetic acid. International Uniform Chemical Information Database.

(b)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [X]; LCL_0 [ ]; Other [ ]
Species/strain:	Mouse
Exposure period:	1 hour
Value:	5,620 ppm
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
Remarks:	Inhalation of > 1,000 ppm produced irritation of the conjunctiva and upper respiratory tract.
Reliability:	Klimisch category 4
References:	Ghiringhelli, L. and Difabio, A. 1957. Med. Lav. 48: 559. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. Volume II, Part E. Toxicology. New York: John Wiley & Sons, Inc.

(c)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [X]; LCL_0 [ ]; Other [ ]
Species/strain:	Rat
Exposure period:	1 hour
Value:	>30 g/m^3
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Reliability:	Klimisch category 4

References: BIOFAX Industrial Bio-Test Laboratories, Inc. 1971. Data sheets. 19-3. In Registry of Toxic Effects of Chemical Substances. 1999. Sodium acetate. National Institute for Occupational Safety and Health.

5.1.3 ACUTE DERMAL TOXICITY

(a)

Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Rabbit
Value: 1060 mg/kg b.w
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid (64-19-7)
Reliability: Klimisch category 4
References: Union Carbide Corporation. 1963. Union Carbide data sheet. Union Carbide Corporation. Industrial Medicine & Technology. In European Commission. 1996. Acetic acid. International Uniform Chemical Information Database.

(b)

Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Rabbit
Value: > 20,000 mg/kg b.w.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Dose was administered via a single skin penetration to three female albino New Zealand rabbits and kept in place by gauze patches under a latex rubber film.
GLP: Yes [ ] No [ ] ? [X]
Test substance: Fumaric Acid (110-17-8)
Remarks: No mortality was observed at the high dose of 20,000 mg/kg b.w.
Reliability: Klimisch category 2
References: Vernot, E.H., MacEwen, J.D., Haun, C.C., and Kinkead, E.R. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42:417-423.

(c)

Type: LD_0 [ ]; LD_{100} [ ]; LD_{50} [ ]; LDL_0 [ ]; Other [X]
Species/strain: Rabbit
Results: 3 minute exposure = very slight erythema (hair on site); no edema
24 and 48 hrs after 3 minute exposure = no erythema and no edema
60 minute exposure = very slight erythema; no edema

	24 and 48 hrs after 60 minute exposure = no erythema; no edema 4hr exposure = very slight-moderate to severe erythema; very slight – moderate edema 24 hrs after 4 hr exposure = very slight-moderate to severe erythema; very slight – moderate edema 48 hrs after 4 hr exposure = Well defined erythema; slight – no edema
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* According to DOT 3-1/10-07-91/REV5 (49 CFR). Young adult, New Zealand White rabbits (five males and three females) were used in this study. The test material was initially applied to one animal for a 3 minute exposure period. Due to the absence of skin corrosion in this initial animal, a second animal was initiated utilizing a 60 minute exposure period. Due to the absence of skin corrosion for the 60 minute exposure period, the test material was ultimately administered to six additional animals for an exposure period of 4 hours. Each animal received on 0.5 ml quantity of undiluted test material each of which was applied in this manner to one intact skin site per animal. Three (3) minute, twenty-four (24), and forty-eight (48) hour skin scores, derived from the intact skin site were evaluated for corrosion in the rabbit receiving a three minute exposure period. Sixty (60) minute, twenty-four (24), and forty-eight(48) hour skin scores, derived from the intact skin site were evaluated for corrosion in the rabbit receiving a sixty minute exposure period. Four (4), twenty-four (24), and forty-eight (48) hour skin scores, derived from the intact skin site were evaluated for corrosion in the rabbit receiving a four hour exposure period.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9), purity: 60%
Remarks:	Corrosion was considered to have occurred if the substance in contact with the intact rabbit skin caused destruction or irreversible alteration of the tissue of two or more rabbits. Tissue destruction was considered to have occurred if, at any of the readings, there was ulceration or necrosis. Test generally follows GLP procedures.
Reliability:	Klimisch category 2

References: Hill Top Biolabs, Inc. 1992. D.O.T. corrosivity potential study in rabbits of : Citric acid solution, 60% for Cargill, Inc. Hill Top Biolabs project No. 92-8758-21 (A). Cargill, Inc. Project No. ED76904.

5.1.4 ACUTE TOXICITY BY OTHER ROUTES OF ADMINISTRATION

(e.g. subcutaneous, intravenous, etc.)

(a)

Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]

Species/strain: Mouse

Route of Administration: i.m. [ ]; i.p. [ ]; i.v. [X]; Infusion [ ]; s.c. [ ]; Other [ ]

Value: 525 mg/kg b.w.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated

GLP: Yes [ ] No [ ] ? [X]

Test substance: Acetic Acid (64-19-7)

References: Oro, L. and Wretlind, A. 1961. Acta Pharmacol. 18:141. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. Volume II, Part E. Toxicology. New York: John Wiley & Sons, Inc.

(b)

Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]

Species/strain: Rat

Route of Administration: i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other [ ]

Value: 632 mg/kg b.w.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated

GLP: Yes [ ] No [ ] ? [X]

Test substance: Acetic Acid, Ammonium Salt (631-61-8)

References: Lewis, R.T. (ed.) 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(c)

Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]

Species/strain: Mouse

Route of Administration: i.m. [ ]; i.p. [ ]; i.v. [X]; Infusion [ ]; s.c. [ ]; Other [ ]

Value: 98 mg/kg b.w.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated

GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid, Ammonium Salt (631-61-8)
References: Lewis, R.T. (ed.) 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(d)
Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Mouse
Route of Administration: i.m. [ ]; i.p. [ ]; i.v. [X]; Infusion [ ]; s.c. [ ]; Other [ ]
Value: 52 mg/kg b.w.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid, Calcium Salt (62-54-4)
References: Welch et al. 1944. J. Lab. Clin. Med. 29:809. In Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(e)
Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Mouse
Route of Administration: i.m. [ ]; i.p. [ ]; i.v. [ ]; Infusion [ ]; s.c. [X]; Other [ ]
Value: 3,200 mg/kg b.w.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Mice were C3H strain and weighed 25 ± 5g.
GLP: Yes [ ] No [X] ? [ ]
Test substance: Acetic Acid, Sodium Salt (127-09-3)
Reliability: Klimisch category 2
References: Allen, H.R., Tucker, R.K., and Geren, C.R. 1986. Potentiation of the toxicity of basic peptides from rattlesnake venoms by acetic acid, sodium salt. Toxicon 24(6):553-558.

(f)
Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [ ]; LDL_0 [ ]; Other [X]
Species/strain: Rat
Route of Administration: i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other []
Results: 10 mg/kg injected intraperitoneally in rats causes hepatotoxicity, tremors, and hypothermia. 100 mg/kg decreases motor activity and causes diuresis.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]

Test substance:	Fumaric Acid (110-17-8)
References:	Mileski, D.R., Kaplan, H.R., Malone, M.H., and Nieforth, K.A. 1965. J. Pharm. Sci. 54: 295. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. 4th Ed. Volume II, Part E: Toxicology. John Wiley & Sons, Inc.

(g)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mouse
Route of Administration:	i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other [ ]
Value:	200 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Analyzed using Behren's method which is described in Statistical Methods in Biological Assay. 1952. p.535.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Fumaric Acid (110-17-8)
Remarks:	Data as cited in Smith. Data from Upjohn Dept of Pharmacology.
Reliability:	Klimisch category 2
References:	Smith, C.G., Grady, J.E., and Northam, J.I. 1963. Relationship between cytotoxicity in vitro and whole animal toxicity. Cancer Chemother. Rep. 30:9-12.

(h)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Route of Administration:	i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other [ ]
Value:	100 mg/kg
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Malic Acid (6915-15-7)
References:	Eastman Kodak. 1981. Health Safety and Human Factors Laboratory, Rochester, New York. In BIBRA. 1992. Toxicology profile: Malic acid and its common salts. BIBRA International.

(i)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Route of Administration:	i.m. [ ]; i.p. [ ]; i.v. [ ]; Infusion [ ]; s.c. [X]; Other [ ]
Value:	5500 mg/kg

Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Six 5-week old male SD-JCL rats weighing 110-140 g were used at each dosage group. A single oral dose was administered for each of a series of concentrations in volumes of 2 ml/100 g body weight. Behavior and mortality were observed for 7 days.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Citric Acid (77-92-9); purity: 99.8% citric acid monohydrate
Remarks:	Observed effects include respiratory failure and emaciation.
Reliability:	Klimisch category 2
References:	Yokotani, H., Usui, T., Nakaguchi, T., Kanabayashi, T. Tanda, M., and Aramaki, Y. 1971. Acute and subacute toxicological studies of TAKEDA-citric acid in mice and rats. J. Takeda Res. lab. 30(1):25-31.

(j)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mouse
Route of Administration:	i.m. [ ]; i.p. [ ]; i.v. [ ]; Infusion [ ]; s.c. [X]; Other [ ]
Value:	2700 mg/kg
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Six 4-week old male ICR-JCL mice weighing 20-24 g were used at each dosage group. A single oral dose was administered for each of a series of concentrations in volumes of 2 ml/100 g body weight. Behavior and mortality were observed for 7 days.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Citric Acid (77-92-9); purity: 99.8% citric acid monohydrate
Remarks:	Observed effects include respiratory failure and emaciation.
Reliability:	Klimisch category 2
References:	Yokotani, H., Usui, T., Nakaguchi, T., Kanabayashi, T. Tanda, M., and Aramaki, Y. 1971. Acute and subacute toxicological studies of TAKEDA-citric acid in mice and rats. J. Takeda Res. lab. 30(1):25-31.

(k)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [ ]; LDL_0 [ ]; Other [X]
Species/strain:	Horse
Route of Administration:	i.m. [ ]; i.p. [ ]; i.v. [X]; Infusion [ ]; s.c. [ ]; Other [ ]
Results:	No significant cardiovascular effects or effects on blood composition in horses injected with 0.56 mg/kg b.w. of citric acid, sodium salt.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Six horses were used.
GLP: Yes [ ] No [ ] ? [X]
Test substance: Citric Acid, Sodium Salt (994-36-5)
References: Hubbell, J.A.E., et al. 1987. Vet. Surg. 16:245. In BIBRA. 1993. Toxicology profile: Citric acid and its common salts. BIBRA International.

(l)
Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Rat
Route of Administration: i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other [ ]
Value: 1,348 mg/kg b.w.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Monosodium citrate (18996-35-5)
References: Journal of Pharmacol. Exp. Therapeutics. 1948. 94:65. In Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(m)
Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Mouse
Route of Administration: i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other [ ]
Value: 1,635 mg/kg b.w.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]
Test substance: Monosodium citrate (18996-35-5)
References: J. of Pharmacol. Exp. Therapeutics. 1948. 94:65. In Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(n)
Type: LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain: Dog
Route of Administration: i.m. [ ]; i.p. [ ]; i.v. [X]; Infusion [ ]; s.c. [ ]; Other [ ]
Value: 167 mg/kg b.w.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Not stated
GLP: Yes [ ] No [ ] ? [X]

Test substance:	Citric Acid, Tripotassium Salt (866-84-2)
References:	American Veterinary Review. 1937. 44:555. In Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.
(o)	
Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Route of Administration:	i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other [ ]
Value:	1,548 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
Remarks:	Effects noted at the high concentrations included convulsions or effect on seizure threshold; cyanosis; changes in structure or function of salivary glands.
Reliability:	Klimisch category 4
References:	J. of Pharmacol. Exp. Therapeutics. 1948. 94:65. In Registry of Toxic Effects of Chemical Substances. 1999. Trisodium citrate. National Institute for Occupational Safety and Health.
(p)	
Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mouse
Route of Administration:	i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other [ ]
Value:	1,364 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
Remarks:	Effects noted at the high concentrations included convulsions or effect on seizure threshold; cyanosis; changes in structure or function of salivary glands.
Reliability:	Klimisch category 4
References:	J. of Pharmacol. Exp. Therapeutics. 1948. 94:65. In Registry of Toxic Effects of Chemical Substances. 1999. Trisodium citrate. National Institute for Occupational Safety and Health.
(q)	
Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mouse
Route of Administration:	i.m. [ ]; i.p. [ ]; i.v. [X]; Infusion [ ]; s.c. [ ]; Other [ ]

Value:	170 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
Remarks:	Effects noted at the high concentrations included convulsions or effect on seizure threshold; cyanosis; changes in structure or function of salivary glands.
Reliability:	Klimisch category 4
References:	J. of Pharmacol. Exp. Therapeutics. 1948. 94:65. In Registry of Toxic Effects of Chemical Substances. 1999. Trisodium citrate. National Institute for Occupational Safety and Health.

(r)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rabbit
Route of Administration:	i.m. [ ]; i.p. [ ]; i.v. [X]; Infusion [ ]; s.c. [ ]; Other [ ]
Value:	449 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
Remarks:	Effects noted at the high concentrations included convulsions or effect on seizure threshold; cyanosis; changes in structure or function of salivary glands.
Reliability:	Klimisch category 4
References:	J. of Pharmacol. Exp. Therapeutics. 1948. 94:65. In Registry of Toxic Effects of Chemical Substances. 1999. Trisodium citrate. National Institute for Occupational Safety and Health.

(s)

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mouse
Route of Administration:	i.m. [ ]; i.p. [ ]; i.v. [X]; Infusion [ ]; s.c. [ ]; Other [ ]
Value:	111 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Magnesium Salt (142-72-3)
Reliability:	Klimisch category 4
References:	J. Clin. Lab. Med. 1944. 29: 804. In Registry of Toxic Effects of Chemical Substances. 2000. Acetic acid, magnesium salt. National Institute for Occupational Safety and Health.

5.4 REPEATED DOSE TOXICITY

(a)

Species/strain:	Rat
Sex:	Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral
Exposure period:	8 months
Frequency of treatment:	3 times per week
Dose:	0.5 ml of 3% water solution of acetic acid (about 60 mg/kg bw/treatment)
Control group:	Yes [ ]; No [X]; No Data [ ] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results:	As expected, rats treated with the carcinogen NSEE had high incidences of pre-neoplastic lesions of the esophagus and forestomach, as well as benign tumors, carcinomas and squamous cell cancer. Prolonged administration of acetic acid in combination with NSEE resulted in an increase in the number of benign and malignant tumors and carcinomas in the esophagus. Prolonged administration of acetic acid alone did not induce tumors. All nine of these rats, however, did experience hyperplasia in the esophagus and forestomach.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Nine outbred white male rats weighing approximately 100 g were used in the acetic acid alone study. Rats were given either N-nitrosarcosin ethyl ester (NSEE; a known carcinogen) alone, NSEE with the acetic acid solution, or the acetic acid solution alone. All doses were given by intubation into the esophagus. Animals were killed by ether inhalation after 8 months of experiments and autopsied.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic acid (64-17-9)
Reliability:	Klimisch category 2
References:	Alexandrov, V.A., Novikov, A.I., Zabezhinsky, M.A., Stolyarov, V.I., and Petrov, A.S. 1989. The stimulating effect of acetic acid, alcohol, and thermal burn injury on esophagus and forestomach carcinogenesis induced by n-nitrososarcosin ethyl ester in rats. Cancer Lett. 47:79-185.

(b)

Species/strain:	Rat and mouse
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No Data [X]
Route of Administration:	Inhalation
Exposure period:	3-35 days
Frequency of treatment:	Continuous

Dose:	11-35 ppm
Control group:	Yes [ ]; No [ ]; No Data [X] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results:	At 15 ppm (for 22 days) or more, the animals showed decreased activity, behavioral changes and reduced work capacity. At 23-31 ppm (17-35 days), there was decreased growth, increased spleen weight, an increase of the level of iron stored in the spleen, signs of kidney damage and increased kidney weights.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Groups of at least 10 rats and 10 mice were used.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
Reliability:	Klimisch category 2
References:	Savina, V.P. and Anisimov, B.V. 1987. Kosm. Biol. Aviakosm. Med. 21:79. In BIBRA. 1993. Toxicology profile: Acetic acid and its common salts. BIBRA International.

(c)

Species/strain:	Rat (Long-Evans hooded)
Sex:	Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral (in drinking water)
Exposure period:	8 months
Frequency of treatment:	daily *ad libitum*
Dose:	50 and 500 ppm
Control group:	Yes [ ]; No [X]; No Data [ ] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
NOAEL:	500 ppm
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Long-Evans hooded rats 21 days old at test initiation were used. The test material was administered *ad libitum* for eight months.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Remarks:	No significant effects on survival, reinforcement behavior, or body weight gain were observed. The rats treated with acetic acid, sodium salt served as the control for a lead exposure study. Therefore, no separate untreated controls are available for comparison.
Reliability:	Klimisch category 2
References:	Cory-Slechta, D.A. 1986. Neurobehav. Toxicol. Teratol. 8:237-244. In European Commission. 1996. Sodium acetate. International Uniform Chemical Information Database.

(d)

Species/strain:	Rat
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No Data [X]
Route of Administration:	oral in diet
Exposure period:	4 weeks
Frequency of treatment:	daily
Dose:	3.58% of the diet (approx. 3.6 g/kg b.w./day)
Control group:	Yes [ ]; No [ ]; No Data [X] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results:	Growth and survival were normal.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* 13 young rats were used.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Reliability:	Klimisch category 2
References:	Dryden, L.P. and Hartman, A.M. 1971. J. Nutr. 101:589. In BIBRA. 1993. Toxicology profile: Acetic acid and its common salts. BIBRA International.

(e)

Species/strain:	Rat
Sex:	Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral in drinking water
Exposure Period:	112 days, beginning at 31 days of age
Frequency of treatment:	Continuous
Dose:	100 ppm
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
Results:	No mortality or cognitive impairment was observed.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Eight young adult male Wistar rats were exposed to acetic acid, sodium salt in their drinking water. Training in mazes began on day 112 and lasted until day 157 at which time all animals were sacrificed.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Remarks:	The rats treated with acetic acid, sodium salt served as the control for a lead exposure study. Therefore, no untreated controls are available for comparison.
Reliability:	Klimisch category 2
References:	Massaro, E.J. and Massaro, T.F. 1987. Low level lead exposure during neonatal development perturbs cognitive function. J. Am. Coll. Toxicol. 6(4):441-450.

(f)

Species/strain:	Rat
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No Data [X]
Route of Administration:	oral in diet
Exposure period:	3 months
Frequency of treatment:	daily
Dose:	21 mg/kg b.w./day
Control group:	Yes [ ]; No [ ]; No Data [X] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results:	Indications of altered thyroid function and decreased growth were reported.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Ten rats were used.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Reliability:	Klimisch category 2
References:	Goldman, M. 1981. Experientia 37:1348. In BIBRA. 1993. Toxicology profile: Acetic acid and its common salts. BIBRA International.

(g)

Species/strain:	Rat
Sex:	Female [ ]; Male [ ]; Male/Female [X]; No Data [ ]
Route of Administration:	oral in diet
Exposure period:	2 years
Frequency of treatment:	daily
Dose:	female and male rats: 0.1, 0.5, 0.8 or 1.2% fumaric acid male rats: 0.5, 1, or 1.5% fumaric acid
Control group:	Yes [ ]; No [ ]; No Data [X] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results:	Slightly increased mortality and increased incidence of testes degeneration were observed in rats fed 1.5% fumaric acid (approximately 750 mg/kg b.w/day). Two rats receiving 1% or 0.5% had stomach inflammation.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Groups of 12 male and 12 female rats or groups of just male rats were fed the stated doses in the diet.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 2
References:	Fitzhugh, O.G. and Nelson, A.A. 1947. J. Am. Pharm. Assoc. 36:217. In BIBRA. 1991. Toxicology profile: Fumaric acid and its common salts. BIBRA International.

(h)

Species/strain:	Rat
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No Data [X]
Route of Administration:	Oral
Exposure period:	2 years
Frequency of treatment:	Daily
Dose:	0.05, 0.5 or 5% in diet (equivalent to 2-200 mg/kg bw/day)
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results:	No tissue abnormalities or changes in the blood or urine were observed. Changes in organ weights, and in the first year, decreased growth, and hunched appearance were observed in rats receiving 200 mg/kg bw/day.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Malic Acid (6915-15-7)
Remarks:	The percent in diet is stated to be equivalent to 2-200 mg kg b.w./day, but BIBRA notes that the values in the region of 25-2,500 mg/kg b.w./day seem more likely.
Reliability:	Klimisch category 2
References:	Hazleton Laboratories. 1971. 24-Month dietary administration-rats and 104-week dietary administration-dogs [Material X-5120]. Final reports submitted to Allied Chemical Corporation, Buffalo, New York. In BIBRA. 1992. Toxicology profile: Malic acid and its common salts. BIBRA International.

(i)

Species/strain:	Rabbit
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No Data [X]
Route of Administration:	oral in diet
Exposure period:	150 days
Frequency of treatment:	daily
Dose:	7.7% citric acid, sodium salt (~5% free acid)
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
Results:	No gross or histopathological changes or difference in growth or survival found.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Rabbits were exposed to citric acid, sodium salt in the diet for 150 days.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)
Reliability:	Klimisch category 2

References: Packman, E.W., Abbott, D.D., and Harrison, J.W.E. 1963. Toxicol. Appl. Pharmacol. 5:163. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. 4th Ed. Volume II, Part E: Toxicology. John Wiley & Sons, Inc.

(j)

Species/strain: Rat (Sprague-Dawley)
Sex: Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]
Route of Administration: oral in diet
Exposure period: 6 weeks
Frequency of treatment: daily
Post exposure observation period: none
Dose: 0.2, 2.4, and 4.8%
Control group: Yes [X]; No [ ]; No Data [ ]
Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
NOEL: 2,260 mg/kg bw
LOAEL: 4,670 mg/kg bw
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Male SD-JCL rats weighing 98 to 112 g, and 29 to 35 days old at test initiation were fed citric acid in the diet. Four groups of 10 animals each were maintained at 23 ± 1°C for 6 weeks. Body weight was measured in all animals 2 times per week, food intake was measured in a group of five animals twice per week, and any behavioral abnormalities were observed daily.
GLP: Yes [ ] No [X] ? [ ]
Test substance: Citric Acid (77-92-9); purity: 99.8% citric acid monohydrate
Remarks: No behavioral abnormalities, effects on body weight gain, or mortality were observed. Some minor biochemical changes were observed with the highest dose, but no specific pathohistological abnormalities were detected.
Reliability: Klimisch category 2
References: Yokotani, H., Usui, T., Nakaguchi, T., Kanabayashi, T. Tanda, M., and Aramaki, Y. 1971. Acute and subacute toxicological studies of TAKEDA-citric acid in mice and rats. J. Takeda Res. lab. 30(1):25-31.

(k)

Species/strain: Rat
Sex: Female [ ]; Male [ ]; Male/Female [ ]; No Data [X]
Route of Administration: oral in diet
Exposure period: ~ 1 year
Frequency of treatment: daily
Dose: 0.1%

Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
Results:	No adverse effects were found.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Two successive generations of rats were fed 0.1% citric acid, sodium salt in the diet.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Sodium Salt (994-36-5)
Remarks:	A limited number of tissues were examined microscopically.
Reliability:	Klimisch category 2
References:	Bonting, S.L., and Jansen, B.C.P. 1956. Voeding 17: 137. In BIBRA. 1993. Toxicology profile: Citric acid and its common salts. BIBRA International.

(l)

Species/strain:	Rat
Sex:	Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral in diet
Exposure period:	32 weeks
Frequency of treatment:	daily
Dose:	5% (~2,500 mg/kg b.w./day)
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
Results:	No overt signs of toxicity were observed.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Twenty male rats were fed 5% citric acid, sodium salt in the diet for 32 weeks (about 2,500 mg/kg b.w./day).
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Sodium Salt (994-36-5)
Reliability:	Klimisch category 2
References:	Fukushima, S., et al. 1986. Gann 77:1. In BIBRA. 1993. Toxicology profile: Citric acid and its common salts. BIBRA International

(m)

Species/strain:	Mouse
Sex:	Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral feed
Exposure period:	12 months
Frequency of treatment:	Continuous in the diet
Post exposure observation period:	None
Dose:	2 g Mn/kg of food in the form of acetic acid, manganese salt
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]

Results:	No mortality was observed during the experiment. By the end of the study, body weight gain was significantly suppressed in the treatment mice compared to the controls (P<0.05). When body weight gain became less than that of the control, changes in spontaneous motor activity were noted. In the hypothalamus, dopamine levels decreased significantly (P< 0.05) and the manganese content increased up to 13 times compared to the controls.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Six-week old male ddY mice weighing 29.1± 0.2 g were divided into two groups with six mice in each. The first group served as the control and the second received 2 g Mn/kg in the form of acetic acid, manganese salt in the diet for twelve months. All animals were allowed free access to food and water. Body weight changes were recorded and spontaneous motor activity was tested. Urine, blood, and tissue samples were analyzed. Mice were decapitated 24 hours after last feeding.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Manganese Salt (638-38-0)
Reliability:	Klimisch category 2
References:	Komura, J. and Sakamoto, M. 1992. Effects of manganese forms on biogenic amines in the brain and behavioral alterations in the mouse: Long-term oral administration of several manganese compounds. Environ. Res. 57(1):34-44.

5.5 GENETIC TOXICITY *IN VITRO*

A. Bacterial Test

(a)

Type:	Bacterial reverse mutation assay
System of testing:	TA 98, TA 100, TA 1535, TA 1537, and TA 1538
Metabolic activation:	With [ ]; Without [ ]; With and Without [X]; No Data [ ]

Results:

Genotoxic effects:	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Ames test
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid (64-19-7)
Reliability:	Klimisch category 2

References: NcMahon et al. 1979. Cancer Res. 39:682-693. In European Commission. 1996. Acetic acid. International Uniform Chemical Information Database.

(b)

Type: Bacterial reverse mutation assay

System of testing: *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 97 and/or TA 1537.

Concentration: 100, 333, 1000, 3333, 6666, 10000 µg/plate

Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No Data [ ]

Results:

Genotoxic effects:	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]* Standard Ames test.

GLP: Yes [X] No [ ] ? [ ]

Test substance: Acetic Acid (64-19-7), purity: 99%

Remarks: Tested within the National Toxicology Program's mutagenicity testing program.

Reliability: Klimisch category 1

References: Zeiger, E., Anderson, B., Haworth, S. Lawlor, T., and Mortelmans, K. 1992. Salmonella mutagenicity test: V. results from the testing of 311 chemicals. Environ. Mol. Mutagen. 19(Suppl. 21):2-141.

(c)

Type: Bacterial reverse mutation assay

Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No Data [ ]

Results: Acetic acid and its sodium and zinc salts have given no evidence of mutagenic activity in good-quality Ames tests using *Salmonella typhimurium* either with or without S9.

Genotoxic effects:	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]* Ames test

GLP: Yes [ ] No [ ] ? [X]

Test substance: Acetic Acid (64-19-7); Acetic Acid, Sodium Salt (127-09-3)

Reliability: Klimisch category 2

References: BIBRA. 1993. Toxicology profile: Acetic acid and its common salts. BIBRA International.

(d)

Type:	Bacterial reverse mutation assay
System of testing:	*Salmonella typhimurium* strains TA 92, TA 94, TA 98, TA 100, TA 1535, and TA 1537,
Concentration:	maximum concentration of 40 mg/plate
Metabolic activation:	With [X]; Without [ ]; With and Without [ ]; No Data [ ]
Results:	
Genotoxic effects:	+ ? -
	With metabolic activation: [ ] [ ] [X]
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* An Ames test was conducted using the test substance in a phosphate buffer. Six concentrations were tested. Two plates were used for each concentration.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Reliability:	Klimisch category 2
References:	Ishidate, M., Jr., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., and Matsouka, A. 1984. Primary mutagenicity screening of food additives currently used in Japan. Fd. Chem. Toxic. 22(8):623-636.

(e)

Type:	Bacterial reverse mutation assay
System of testing:	*Salmonella typhimurium* strains TA 98, TA100, TA 1535, TA 97 and/or TA1537
Concentration:	Not stated
Metabolic activation:	With [ ]; Without [ ]; With and Without [X]; No Data [ ]
Results:	
Genotoxic effects:	+ ? -
	With metabolic activation: [ ] [ ] [X]
	Without metabolic activation: [ ] [ ] [X]
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Ames test.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 2
References:	Zeiger, E., et al. 1988. Environ. Molec. Mutagen. 11:1. In BIBRA. 1991. Toxicology profile: Fumaric acid and its common salts. BIBRA International.

(f)

Type:	Bacterial reverse mutation assay
System of testing:	*Salmonella typhimurium* strain TA 100
Concentration:	1000, 100, 10, 1, and 0.1 µg/plate
Metabolic activation:	With [ ]; Without [X]; With and Without [ ]; No Data [ ]

Results:

Genotoxic effects:

	+	?	-
Without metabolic activation:	[ ]	[ ]	[X]

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
An Ames test was conducted using a constant volume of 0.4 ml of fumaric acid at concentrations of 1000, 100, 10, 1, and 0.1 µg/plate.

GLP: Yes [ ] No [ ] ? [X]
Test substance: Fumaric Acid (110-17-8)
Reliability: Klimisch category 2
References: Rapson, W.H., Nazar, M.A., and Butsky, V.V. 1980. Mutagenicity produced by aqueous chlorination of organic compounds. Bull. Environm. Toxicol. 24:590-596.

(g)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* strains TA 97, TA 98, TA 100, and TA 104
Concentration: 0, 1100, 1500, and 2000 µg/plate
Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No Data [ ]

Results:

Genotoxic effects:

	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Ames Salmonella/microsome test. All tests were done in triplicate both with and without S9 activation.

GLP: Yes [ ] No [ ] ? [X]
Test substance: Malic Acid (6915-15-7)
Reliability: Klimisch category 2
References: Al-Ani, F.Y. and Al-Lami, S.K. 1988. Absence of mutagenic activity of acidity regulators in the ames salmonella/microsome test. Mutat. Res. 206:467-470.

(h)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* strains TA 97, TA 98, TA 100, and TA 104
Concentration: 0, 500, 1000, and 2000 µg/plate
Metabolic activation: With [ ]; Without [ ]; With and Without [X]
Results:

Genotoxic effects:

	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Ames *Salmonella*/microsome test. All tests were done in triplicate both with and without S9.

GLP: Yes [ ] No [ ] ? [X]

Test substance: Citric Acid (77-92-9)

Reliability: Klimisch category 2

References: Al-Ani, F.Y. and Al-Lami, S.K. 1988. Absence of mutagenic activity of acidity regulators in the Ames *Salmonella*/microsome test. Mutat. Res. 206:467-470.

(i)

Type: Cytogenetic assay

System of testing: *S. cerevisiae* cells

Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No Data [ ]

Results:

Genotoxic effects:

	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Ames test

GLP: Yes [ ] No [ ] ? [X]

Test substance: Citric Acid, Sodium Salt (994-36-5); Citric Acid, Tripotassium Salt (866-84-2)

Reliability: Klimisch category 2

References: Litton Bionetics Inc. 1975. Contract No. 223-74-2104 and FDA 71-268. In BIBRA. 1993. Toxicology Profile: Citric acid and its common salts. BIBRA International.

(j)

Type: Bacterial reverse mutation assay

System of testing: *Salmonella typhimurium* strains TA 92, TA 1535, TA 100, TA 1537, TA 94, and TA 98.

Concentration: maximum dose of 5.0 mg/plate

Metabolic activation: With [X]; Without [ ]; With and Without [ ]; No Data [ ]

Results:

Genotoxic effects:

	+	?	-
With metabolic activation:	[ ]	[ ]	[X]

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
An Ames test was conducted using monosodium citrate (18996-35-5) in a phosphate buffer. Six concentrations were tested. Two plates were used for each concentration.

GLP: Yes [ ] No [ ] ? [X]

Test substance: Monosodium citrate (18996-35-5), purity: 99.6%

Reliability: Klimisch category 2

References: Ishidate, M., Jr., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T. Sawada, M., and Matsouka, A. 1984. Primary mutagenicity screening of food additives currently used in Japan. Fd. Chem. Toxic. 22(8):623-636.

(k)
Type: Bacterial gene mutation *(*Rec-assay)
System of testing: *Bacillus subtillus* strains H17 (Rec^+, arg^- ,and trp^-) and M45 (Rec^+, arg^-,and trp^-)
Concentration: 0.05 M
Results: < 5 mm distance (weakly positive)
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
Each assay was repeated three times. An 0.05 aliquot of acetic acid, manganese salt (0.05 M) was dropped onto a 10 mm diameter filter paper disk. Plates were incubated at 37°C for 24 hours. The inhibition of growth is indicated by the distance (mm) between the edge of a paper disc and that of streaks. The difference between the inhibition zones for Rec^+ and Rec^- cells may be due to cellular repair. This is called "rec-effect".
GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid, Manganese Salt (638-38-0),
Reliability: Klimisch category 2
References: Nishioka, H. 1975. Mutagenic activities of metal compounds in bacteria. Mutat. Res. 31:185-189.

B. Non-bacterial *in vitro* test

(a)
Type: Cytogenetic assay
Concentration: ≤16 mM
System of testing: Chinese hamster ovary K1 cells
Results: Acetic acid was not clastogenic at concentrations close to those showing cytotoxicity.
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*
CHO test guideline
GLP: Yes [ ] No [ ] ? [X]
Test substance: Acetic Acid (64-19-7)
Remarks: Low pH did induce some artificial chromosome aberrations, but these were eliminated by neutralization of the test medium.
Reliability: Klimisch category 2
References: Morita, T. Takeda, K., and Okumura, K. 1990. Mutat. Res. 240:195. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. 4th Ed. Volume II, Part E: Toxicology. John Wiley & Sons, Inc.

(b)

Type:	Cytogenetic assay
System of testing:	Chinese hamster fibroblast cell line
Concentration:	maximum dose of 1 mg/ml
Metabolic activation:	With [ ]; Without [X]; With and Without [ ]; No Data [ ]
Results:	
Genotoxic effects:	+ ? -
	Without metabolic activation: [ ] [ ] [X]
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Substance was tested in a physiological saline solvent. Three different concentrations were tested and cells were exposed to each concentration for 48 hours.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Reliability:	Klimisch category 2
References:	Ishidate, M., Jr., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T. Sawada, M., and Matsouka, A. 1984. Primary mutagenicity screening of food additives currently used in Japan. Fd. Chem. Toxic. 22(8):623-636.

(c)

Type:	Cytogenetic assay
System of testing:	Chinese hamster fibroblast cell line
Concentration:	maximum dose of 0.5 mg/ml
Metabolic activation:	With [ ]; Without [X]; With and Without [ ]; No Data [ ]
Results:	
Genotoxic effects:	+ ? -
	Without metabolic activation: [ ] [ ] [X]
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Substance was tested in a physiological saline solvent. Three different concentrations were tested and cells were exposed to each concentration for 24 hours.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Fumaric Acid (110-17-8), purity: 99.7%
Reliability:	Klimisch category 2
References:	Ishidate, M., Jr., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T. Sawada, M., and Matsouka, A. 1984. Primary mutagenicity screening of food additives currently used in Japan. Fd. Chem. Toxic. 22(8):623-636.

(d)

Type:	Cytogenetic assay
System of testing:	Chinese hamster fibroblast cell line
Concentration:	maximum dose of 1 mg/ml

Metabolic activation:	With [ ]; Without [X]; With and Without [ ]; No Data [ ]
Results:	
Genotoxic effects:	+ ? -
	Without metabolic activation: [ ] [ ] [X]
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Substance was tested in a physiological saline solvent. Three different concentrations were tested and cells were exposed to each concentration for 48 hours.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Malic Acid (6915-15-7)
Reliability:	Klimisch category 2
References:	Ishidate, M., Jr., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T. Sawada, M., and Matsouka, A. 1984. Primary mutagenicity screening of food additives currently used in Japan. Fd. Chem. Toxic. 22(8):623-636.

5.6 GENETIC TOXICITY *IN VIVO*

(a)

Type:	Testicular DNA-synthesis inhibition test
Species/strain:	Mouse
Sex:	Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]
Route of Administration:	gavage
Exposure period:	single application
Doses:	200, 500, and 1,000 mg/kg
Results:	No inhibitory effect on DNA-replication was detectable.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* 3H-thymidine incorporation was measured.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Remarks:	This is not a standard genotoxicity test system, but it provides evidence that acetic acid, sodium salt is not genotoxic in animals.
Reliability:	Klimisch category 2
References:	Seiler, J.P. 1981. The testicular DNA-synthesis inhibition test (DSI Test). In Short Tests Chem Carcinogen. In European Commission. 1996. Sodium acetate. International Uniform Chemical Information Database.

(b)

Type:	Dominant lethal assay
Species/strain:	Rat
Sex:	Female [ ]; Male [ ]; Male/Female [X]; No Data [ ]
Route of Administration:	Not stated
Exposure period:	5 days

Doses:	3 g/kg
Results:	No mutagenic potential was detected.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)
Reliability:	Klimisch category 4
References:	Litton Bionetics, Inc. 1975. Contract No. FDA 71-268. In European Commission. 1996. Fumaric acid. International Uniform Chemical Information Database.

5.8 TOXICITY TO REPRODUCTION

(a)

Type:	Fertility [ ]; One-generation study [X]; Two-generation study [ ]; Other [ ]
Species/strain:	Guinea pig
Sex:	Female [ ]; Male [ ]; Male/Female [X]; No Data [ ]
Route of Administration:	oral in feed
Frequency of treatment:	daily
Doses:	1% (~ 400 mg/kg b.w./ day)
Control group:	Yes [ ]; No [X]; No Data [ ] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
NOEL Parental:	400 mg/kg bw/ day
NOEL F1 Offspring:	400 mg/kg bw/ day
Results:	There were no detectable toxic effects on growth, reproduction or lactation.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Two pregnant females received fumaric acid in their diet. Combined, they produced 12 offspring. The males were also fed fumaric acid in the diet.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 4
References:	Levey, S. et al. 1946. J. Am. Pharm. Assoc. 35:298. In European Commission. 1996. Fumaric acid. International Uniform Chemical Information Database.

(b)

Type:	Fertility [X]; One-generation study [ ]; Two-generation study [ ]; Other [ ]
Species/strain:	Rat
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral in diet
Exposure period:	several months
Frequency of treatment:	daily
Doses:	600 mg/kg b.w

Control group:	Yes [ ]; No [ ]; No Data [X] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
NOAEL:	= 600 mg/kg bw
LOAEL:	>600 mg/kg bw
Results:	No reproductive effects detected.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Rats were fed diets containing 1.2% citric acid (about 600 mg/kg bw/ day). Exposure began 29 weeks prior to mating and continued for a few months after mating.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)
Reliability:	Klimisch category 2
References:	Bonting and Jansen. 1956. Voeding 17:137. In European Commission. 1996. Citric acid. International Uniform Chemical Information Database. Also, In BIBRA. 1993. Toxicology profile: Citric acid and its common salts. BIBRA International.

(c)

Type:	Fertility [X]; One-generation study [X]; Two-generation study [ ]; Other [ ]
Species/strain:	Rat and mouse
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral in diet
Frequency of treatment:	daily
Doses:	5%
Control group:	Yes [ ]; No [ ]; No Data [X] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results:	No effects on reproduction, litter size or survival up to weaning were detected. A decrease in body weight gain and reduced survival time in mice were observed.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Female rats and mice were fed diets containing 5% citric acid (about 2.5 g/kg bw/day) before, during, and after mating.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)
Remarks:	The effects on body weight gain and survival time may have resulted from the chelating ability of citric acid, which could impair absorption of calcium and iron.
Reliability:	Klimisch category 2
References:	Wright, E. and Hughes, R.E. 1976. Nutr. Rep. Int. 13:563. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. 4th Ed. Volume II, Part E: Toxicology. John Wiley & Sons, Inc.

(d)

Type:	Fertility [X]; One-generation study [ ]; Two-generation study [ ]; Other [ ]
Species/strain:	Rat
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral in diet
Exposure period:	several months
Frequency of treatment:	daily
Doses:	0.1% citric acid, sodium salt
Control group:	Yes [ ]; No [ ]; No Data [X] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
NOAEL:	0.1% citric acid, sodium salt
LOAEL:	>0.1% citric acid, sodium salt
Results:	No reproductive effects detected at 0.1% citric acid, sodium salt.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Rats were fed diets containing 0.1% citric acid, sodium salt. Exposure began 29 weeks prior to mating and continued for a few months after mating.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Sodium Salt (994-36-5)
Reliability:	Klimisch category 2
References:	Bonting and Jansen. 1956. Voeding 17:137. In BIBRA. 1993. Toxicology profile: Citric acid and its common salts. BIBRA International.

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

(a)

Species/strain:	Mouse
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral
Duration of the test:	17 days
Exposure period:	10 days
Frequency of treatment:	daily
Doses:	0, 16, 74, 345, and 1600 mg/kg bw/day
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
Results:	No effects on nidation or on maternal or fetal survival at doses up to 1600 mg/kg bw/day
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Following mating, adult female albino CD-1 mice were dosed daily by oral intubation beginning on day 6 of gestation. Animals were observed daily and body weights recorded for 10 days. On day 17, Caesarian sections were performed on all dams and the numbers of

	implantation sites, resorption sites, and live and dead fetuses was recorded. General external and internal examinations were also made of the dams.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid (64-19-7)
Reliability:	Klimisch category 2
References:	Food and Drug Research Laboratories. 1974. Teratologic Evaluation of FDA 71-78 (Apple Cider Vinegar; Acetic Acid; Table Strength 5%) in Mice, Rats and Rabbits. NTIS PB234869.

(b)

Species/strain:	Rat
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral
Duration of the test:	14 days
Exposure period:	10 days
Frequency of treatment:	daily
Doses:	0, 16, 74, 345, and 1600 mg/kg bw/day
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
Results:	No effects on nidation or on maternal or fetal survival at doses up to 1600 mg/kg bw/day
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Following mating, adult female albino rats (Wistar) were dosed daily by oral intubation beginning on day 6 of gestation. Animals were observed daily and body weights recorded. On day 20, Caesarian sections were performed on all dams and the numbers of implantation sites, resorption sites, and live and dead fetuses was recorded. General external and internal examinations were also made of the dams.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid (64-19-7)
Reliability:	Klimisch category 2
References:	Food and Drug Research Laboratories. 1974. Teratologic Evaluation of FDA 71-78 (Apple Cider Vinegar; Acetic Acid; Table Strength 5%) in Mice, Rats and Rabbits. NTIS PB234869.

(c)

Species/strain:	Rabbit
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral
Duration of the test:	23 days
Exposure period:	13 days
Frequency of treatment:	daily
Doses:	0, 16, 74, 345, and 1600 mg/kg bw/day

Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
Results:	No effects on nidation or on maternal or fetal survival at doses up to 1600 mg/kg bw/day
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Following artificial insemination, adult Dutch-belted female rabbits were dosed daily by oral intubation beginning on day 6 of gestation. Animals were observed daily and body weights recorded. On day 29, Caesarian sections were performed on all does and the numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses was recorded. General external and internal examinations were also made of the does.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid (64-19-7)
Reliability:	Klimisch category 2
References:	Food and Drug Research Laboratories. 1974. Teratologic Evaluation of FDA 71-78 (Apple Cider Vinegar; Acetic Acid; Table Strength 5%) in Mice, Rats and Rabbits. NTIS PB234869.

(d)

Species/strain:	Mouse
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral
Exposure period:	5 days (days 8-12 of gestation)
Frequency of treatment:	daily
Post exposure observation period:	~ 2weeks
Duration of the test	~ 3 weeks
Doses:	1,000 mg/kg b.w.
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [ ]; Concurrent vehicle [X]; Historical [ ]
NOEL Parental:	1,000 mg/ kg b.w.
NOEL F1 Offspring:	1,000 mg/kg b.w.
Results:	General parental toxicity: No effects Toxicity to offspring: No effects
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* 30 pregnant CD-1 mice, approximately 60 days old, were give a single oral dose by gavage on days 8-12 of gestation. Animal quarters were maintained at a temperature of 22 °C, a relative humidity of 40-60%, and a 7 am to 7 pm photoperiod.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Reliability:	Klimisch category 2

References:	Kavlock, R.J., Short, R.D., Jr., and Chernoff, N. 1987. Further evaluation of an *in vivo* teratology screen. Teratog. Carcinog. Mutagen. 7:7-16.

(e)

Species/strain:	Fertile single-comb white leghorn chicken eggs
Route of Administration:	injection into egg
Frequency of treatment:	single injection
Doses:	maximum 10.0 mg/egg
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [X]; Historical [ ]
LD_{50}:	4.58 mg/egg
NOAEL teratogenicity:	10.0 mg/egg
Results:	No teratogenic response under any of the four test conditions was observed at the highest concentration injected.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Fertile eggs from single-comb white leghorn chickens were used. The test substance in water was administered by two routes, injection via the yolk and via the air cell. For each injection route, eggs were treated at two stages of incubation: preincubation (0 hrs) and on the fourth day (96 hrs). At least 100 embryos per each of four dose levels were treated. After treatment, all eggs were candled daily and nonviable embryos were removed. Surviving embryos were allowed to hatch.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Remarks:	The LD_{50} is for the test condition in which the injection was made to the yolk sac at 0 hrs.
Reliability:	Klimisch category 3 (non-standard test organism)
References:	Verrett, M.J., Scott, W.F., Reynaldo, E.F., Alterman, E.K., and Thomas, C.A. 1980. Toxicity and teratogenicity of food additive chemicals in the developing chicken embryo. Toxicol Appl. Pharmacol. 56:265-273.

(f)

Type:	*Drosophila* embryonic cell culture test
Species/strain:	*Drosophila* (fruit fly)/Oregon R., Canton S_{109}, and Canton S
Doses:	10^{-3} M
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
Results:	The *in vitro* assay for fumaric acid was negative. There was no apparent teratogenic effect.

Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* *Drosophila* eggs were homogenized and the embryonic cells were plated out in cell culture dishes at 8 x 10^5 cells per ml of medium. After allowing time (15-20 min.) for cells to attach to the bottom of the dish, the medium covering the cells was replaced with medium in which the test substance had been dissolved. Embryonic cells were treated with an initial dose of 0.01 of the LD_{50} for adult female *Drosophila*. Cell and tissue differentiation was scored by counting the number of myotubes and neuron clusters (ganglia). An interference in normal cell differentiation (reduction in the number of myotubes and ganglia compared to the controls), was taken to be an indication of teratogenic response. A total of four dishes per trial were scored. The chemical was tested on three or more separate trials. A 50% reduction in the number of either myotubes and/or ganglia is taken as a teratogenic response.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 3 (non-standard study)
References:	Bournias-Vardiabasis, N. Teplitz, R.L., Chernoff, G.F., and Seecof, R., L. 1983. Detection of teratogens in the Drosophila embryonic culture test: Assay of 100 chemicals. Teratology 28:109-122.

(g)

Species/strain:	Fertile single-comb white leghorn chicken eggs
Route of Administration:	injection into egg
Frequency of treatment:	single injection
Doses:	maximum 10.0 mg/egg
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [X]; Historical [ ]
LD_{50}:	0.42 mg/egg
NOAEL teratogenicity:	10.0 mg/egg
Results:	No teratogenic response under any of the four test conditions was observed at the highest concentration injected.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Fertile eggs from single-comb white leghorn chickens were used. The test substance in water was administered by two routes, injection via the yolk and via the air cell. For each injection route, eggs were treated at two stages of incubation: preincubation (0 hrs) and on the fourth day (96 hrs). At least 100 embryos per each of four dose levels were treated. After treatment, all eggs were candled daily and nonviable

	embryos were removed. Surviving embryos were allowed to hatch.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Malic Acid (6915-15-7)
Remarks:	The LD_{50} for the test condition in which the injection was made to the air sac at 96 hrs.
Reliability:	Klimisch category 3 (non-standard study)
References:	Verrett, M.J., Scott, W.F., Reynaldo, E.F., Alterman, E.K., and Thomas, C.A. 1980. Toxicity and teratogenicity of food additive chemicals in the developing chicken embryo. Toxicol Appl. Pharmacol. 56:265-273.

(h)

Type:	Fertility [ ]; One-generation study [X]; Two-generation study [ ]; Other [ ]
Species/strain:	Rat and mouse
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral
Exposure period:	10 days (days 6-15 of pregnancy)
Frequency of treatment:	daily
Doses:	Rat: 350 mg/kg b.w. Mouse: 266 mg/kg b.w.
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
NOEL Parental:	Rat: 350 mg/kg b.w/day Mouse: 266 mg/kg b.w/day
Results:	No treatment-related fetal or maternal toxic effects or increases in fetal malformations were observed.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Pregnant rats and mice were given DL-malic acid by stomach tube at doses up to 350 and 266 mg/kg bw/ day, respectively, on days 6-15 of pregnancy.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Malic Acid (6915-15-7)
Reliability:	Klimisch category 2
References:	Food and Drug Research Laboratories Inc. 1974. Teratologic evaluations of FDA 71-90 in mice and rats. Contract No. FDA 71-260. In BIBRA. 1992. Toxicology profile: Malic acid and its common salts. BIBRA International.

(i)

Species/strain:	Rat
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral
Duration of the test:	10 days
Exposure period:	days 6-15 of gestation
Frequency of treatment:	daily

Doses:	241 mg/kg b.w./day
Control group:	Yes [ ]; No [ ]; No Data [X] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results:	No indication of adverse effects on nidation (fertilization), maternal, or fetal survival.
NOAEL Maternal:	241 mg/kg b.w.
NOAEL Teratogenicity:	241 mg/kg b.w.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)
Remarks:	No further data provided in reference.
Reliability:	Klimisch category 2
References:	Food & Drugs Research Laboratories, Inc. 1973. Teratologic evaluation of FDA 71-54. Contract No. 71-260. In European Commission. 1996. Citric acid. International Uniform Chemical Information Database.

(j)

Species/strain:	Fertile single-comb white leghorn chicken eggs
Route of Administration:	injection into egg
Frequency of treatment:	single injection
Doses:	maximum 10.0 mg/egg
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [X]; Historical [ ]
LD_{50}:	2.06 mg/egg
NOAEL teratogenicity:	10.0 mg/egg
Results:	No teratogenic response under any of the four test conditions was observed at the highest concentration injected.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Fertile eggs from single-comb white leghorn chickens were used. The test substance in water was administered by two routes, injection via the yolk and via the air cell. For each injection route, eggs were treated at two stages of incubation: preincubation (0 hrs) and on the fourth day (96 hrs). At least 100 embryos per each of four dose levels were treated. After treatment, all eggs were candled daily and nonviable embryos were removed. Surviving embryos were allowed to hatch.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Sodium Salt (994-36-5)
Remarks:	The LD_{50} is for the test condition in which the injection was made into the air sac at 96 hrs.
Reliability:	Klimisch category 3 (non-standard study)

References:	Verrett, M.J., Scott, W.F., Reynaldo, E.F., Alterman, E.K., and Thomas, C.A. 1980. Toxicity and teratogenicity of food additive chemicals in the developing chicken embryo. Toxicol Appl. Pharmacol. 56:265-273.

(k)

Species/strain:	Fertile single-comb white leghorn chicken eggs
Route of Administration:	injection into egg
Frequency of treatment:	single injection
Doses:	maximum 10.0 mg/egg
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [X]; Historical [ ]
LD_{50} (Air cell; 0 hrs):	>10.0 mg/egg
LD_{50}(Air cell, 96 hrs):	1.47 mg/egg
LD_{50}(Yolk sac, 0 hrs):	>10.0 mg/egg
LD_{50}(Yolk sac, 96 hrs):	Estimated to be 12.09 mg/egg by extrapolation on the regression line.
Results:	Air cell treatment at preincubation resulted in a high incidence of birds with hypopigmentation of the down. Air cell treatment on the fourth day resulted in a high incidence of birds with severe abnormalities at all 3 test levels that allowed some to hatch. The defects involved primarily the beak, eyes, and eyelids.
Method:	*[e.g. OECD, other (with the year of publication or updating of the method used)]* Fertile eggs from single-comb white leghorn chickens were used. The test substance in water was administered by two routes, injection via the yolk and via the air cell. For each injection route, eggs were treated at two stages of incubation: preincubation (0 hrs) and on the fourth day (96 hrs). At least 100 embryos per each of four dose levels were treated. After treatment, all eggs were candled daily and nonviable embryos were removed. Surviving embryos were allowed to hatch.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Acetic Acid, Manganese Salt (638-38-0)
Remarks:	The author considers the hypopigmentation of down to be a toxic effect rather than a teratogenic one.
Reliability:	Klimisch category 3 (non-standard study)
References:	Verrett, M.J., Scott, W.F., Reynaldo, E.F., Alterman, E.K., and Thomas, C.A. 1980. Toxicity and teratogenicity of food additive chemicals in the developing chicken embryo. Toxicol Appl. Pharmacol. 56:265-273.

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1. General Information

Id 1560-69-6
Date February 6, 2005

Note: Appendix B(1) refers to the IUCLID profile for Propionic Acid

1.0 SUBSTANCE INFORMATION

Generic Name	:	Propionic acid, cobalt salt
Chemical Name	:	Propionic acid, cobalt salt
CAS Registry No.	:	1560-69-6
Component Cas Nos.	:	
EINECS No.	:	216-333-1
Structural Formula	:	$C_6H_{10}O_4Co$
Molecular Weight	:	205.1
Synonyms and Tradenames	:	Cobalt propionate
Reference	:	MSDS dated 3/27/02 prepared by OMG Americas, Inc.

2.1 MELTING POINT

Type	:	
Guideline/method	:	OECD 102
Value	:	none °C
Decomposition	:	
Sublimation	:	
Year	:	2003
GLP	:	Yes
Test substance	:	Cobalt propionate
Method	:	Differential Scanning Caloritmeter
Method detail	:	In the preliminary study the test material was heated from 25°C to 400°C at a rate of 20 K/min and heat absorbed or released was measured. During a second phase the change in endothermic.exothermic changes were measured during three cycles of heating and cooling between 180°C and 260°C. In the a final study used a capillary method with visual end point detection. Test material was packed tighly in a tube and heated at 3 K/min between 150°C and 260°C and with a heating irate increase of 0.5°C between 260°C and 300°C.
Remark	:	**Supporting data for dissociation products:** **Acid:** Melting point for propionic acid is reported to be 22.4°C (See Appendix B(1): 2.1)
Result	:	The item melted under decomposition at about 230°C
Reliability	:	[1] Reliable without restriction
Reference	:	Tognucci, A. 2003. Determination of the Melting Point /melting Point Range of Cobalt Propionate, RCC. LTD Environmental Chemistry and Pharmanalytics, CH-4452 Itingen/Switzerland. RCC Study # 849055 Conducted on behalf of the Metal Carboxylates Coalition.

2.2 BOILING POINT

Type	:	
Guideline/method	:	OECD 103
Value	:	Could not be determined
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	Beuchi Melting Point Tester and Capillary Tube
Method detail	:	Preliminary testing involved placing sample in glasss tubes (with capillaries) and sampels were heated from 25°C to 400°C at a heating rate of 20 k/min. The sample was observed visually. The Main study used the same heating range, but utilized a slower heating rate of 10 K/min. Atmospheric pressure and any change in appearance was noted in the data.
Result	:	Boiling Point/Boiling Poing Range could not be dtermined under the conditions of this test
Remark	:	**Supporting data for dissociation products:** **Acid:** Boiling point for propionic acid is reported to be 140.7 – 141.6°C (See Appendix B(1): 2.2)
Reliability	:	[1] Reliable without restriction
Reference	:	Tognucci, A. 2003. Determination of the Melting Point /melting Point Range of Cobalt Propionate, RCC. LTD Environmental Chemistry and

Pharmanalytics, CH-4452 Itingen/Switzerland. RCC Study # 849056
Conducted on behalf of the Metal Carboxylates Coalition.

2.3 DENSITY

Type	:	
Guideline/method	:	
Value	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Density for propionic acid is reported to be 0.992 g/cm^3 at 20°C (See Appendix B(1): 2.3)
Reliability	:	
Reference	:	

2.4 VAPOR PRESSURE

Type	:	
Guideline/method	:	
Value	:	hPa at °C
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Vapor pressure for propionic acid reported to be 5 hPa at 20°C (See Appendix B(1): 2.4)
Reliability	:	
Reference	:	

2.5 PARTITION COEFFICIENT

Type	:	
Guideline/method	:	
Partition coefficient	:	
Log Pow	:	at °C
pH value	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Log Pow for propionic acid reported to be 0.25 – 0.33 (See Appendix B(1): 2.5)
Reliability	:	

Reference :

2.6.1 SOLUBILITY IN WATER

Type	:	
Guideline/method		OECD 105
Value	:	43.7 mg/L
pH value	:	7.42 to 7.79
concentration	:	
Temperature effects	:	
Examine different pol.	:	
pKa	:	at °C
Description	:	
Stable	:	
Deg. product	:	Propionic acid and Co^{+2}
Year	:	
GLP	:	Yes
Test substance	:	Co propionate
Deg. products CAS#	:	
Method	:	Simplified flask mehod and column elution method
Method detail	:	In a preliminary test cobalt propionate was evaluated using a simplified flask method with an abbreviated equilibration time to determine if the test material had a solubility above or below 10 mg/L. This was established (<10 mg/L) and the definitive test used the column elution method. Glass beads (5.98 g) were weighed and transferred into a round bottom flask (25 ml) and test material (0.123 g) was weighed and added to the flask. The mixture was thoroughly shaken. The loaded beads were were added to elution column which was filled with water. Elution of Co propionate was performed using a circulation pump . Flow rate was adjusted and the column allowed to run until five consecutive samples (1 hr apart) did not differ by more than 30%. A second part of the experiment was conducted at half of the initial flow rate to confirm saturation. Analysis was conducted using atomic absorption spectrophotometry .
Result	:	43.7 mg/L Co propionate based on a measured concentrations of 13.2 mg Co/L (±2.8 mg Co/L)
Remark	:	**Supporting data for dissociation products:** **Acid:**
Reliability	:	[1] Reliable without restriction
Reference	:	Tognucci, A. 2003. Determination of Water Solubility of Cobalt Acetate. RCC, Ltd. Environmental Chemistry & and Pharmanalytics, CH-4452 Intingen/Switzerland, RCC Study #849058

2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	°C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Flash point for propionic acid reported to be 52.3°C (See Appendix B(1): 2.7)

Reliability :
Reference :

3.1.1 PHOTODEGRADATION

Type	:	
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) epsilon (max) epsilon (295)
Conc. of substance	:	at °C
DIRECT PHOTOLYSIS		
Halflife (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The calculated time to 50% degradation by indirect photolysis of propionic acid was 4.7 years at room temperature and a pH of 9 with a rate constant of 0.47 x 10^9 L/mol.sec (See Appendix B(1): 3.1.1)
Reliability	:	
Reference	:	

3.1.2 DISSOCIATION

Type	:	Dissociation constant determination
Guideline/method	:	OECD 112
pKb	:	7.58 and 4.85 at 20°C
Year	:	2002
GLP	:	Yes
Test substance	:	Cobalt propionate, received from OMG Americas, Inc. Purple powder, purity not reported.
Approximate water solubility	:	5000 mg/L as determined visually in preliminary study
Method	:	OECD Guideline 112, Dissociation Constants in Water
Method detail	:	Six replicate samples of cobalt propionate were prepared at a nominal concentration of 0.01 moles/L by dissolving 0.259 grams of test substance in 100 mL of degassed water (ASTM Type II). Each sample was titrated against 0.1 N hydrochloric acid while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the

		equivalence point and the titration was carried past the equivalence point. Values of pK were calculated for a minimum of 10 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.
Result	:	Mean (N = 3) pKb values were 7.58 (SD = 0.0290) and 4.85 (SD= 0.0420) at 20°C
Remark	:	The results indicate that dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).
Reliability	:	[1] Reliable without restriction.
Reference	:	Lezotte, F. And W.B. Nixon, 2002. Determination of the dissocation constant of proprionic acid, cobalt (2+) salt, Wildlife International Ltd., Study No. 534C-122, conducted for the Metal Carboxylates Coalition.

3.2.1 MONITORING DATA

Type of measurement	:	
Media	:	
Concentration	:	
Substance measured	:	
Method	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Propionic acid, calcium salt is widely used as a mold and rope inhibitor in bread and bakery products at levels approx. 2000 ppm. Also used to prevent mold in certain cheeses and on certain fruit and vegetable products. (IUCLID, 2000). Weighted mean concentration added to baked goods 1100 ppm (FASEB, 1979)
Reliability	:	
Reference	:	IUCLID (2000); Federation of American Societies for Experimental Biology (FASEB), Evaluation of the health aspects of propionic acid, calcium propionate, sodium propionate, dilauryl thiodipropionate, and thiodipropionic acid as food ingredients, Report of Select Committee on GRAS substances, prepared for US Food and Drug Administration, 1979. PB80104599 [Subequently referred to as FASEB, 1979]

Additional information: According to the Joint FAO/WHO Expert Committee on Food Additives, the estimate of the acceptable daily intakes for man are given as 0 – 10 mg/kg body weight (unconditional acceptance) and 10 – 20 mg/kg body weight (conditional acceptance). This is calculated as the sum of propionic acid, calcium propionate and sodium propionate. The Expert Commitee stated that there is no reason to believe that propionic acid differs toxicologically from its calcium and sodium salts. (FAO Nutrition Meetings, Report Series No. 40A,B,C, WHO/Food Add./67.29, Toxicological Evaluation of Some Antimicrobials, Antioxidants, Emulsifiers, Stabilizers, Flour-Treatment Agents, Acids and Bases.)

3.3.1 TRANSPORT (Fugacity)

Type	:	
Media	:	
Air	:	% (Fugacity Model Level III)
Water	:	% (Fugacity Model Level III)
Soil	:	% (Fugacity Model Level III)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Year	:	2004

Test substance : Co propionate
Method :
Method detail :
Result :

	Mass Amount (percent)	Half-life (hr)	Emissions (kg/hr)
Air	0.159	281	1000
Water	48.6	900	1000
Soil	51.2	900	1000
Sediment	0.0197	3.6×10^3	0

Persistance time 78 hr

: **Supporting data for dissociation products:**
Acid: For propionic acid, the Henry's law constant is 4.15×10^{-7} atm.m^3/mol at 25°C
Reliability : [2]
Reference : EPIWIN 3.11

3.5 BIODEGRADATION

Type :
Guideline/method :
Inoculum :
Concentration :
Contact time :
Degradation :
Result :
Kinetic of test subst. :
Control substance :
Kinetic :
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method Detail :
Result :
Remark : In the Modified Zahn-Wellens inherent biodegradability test, calcium propionate was found to be biodegradable (100% after 7 days). (See Appendix B(1): 3.5)
Supporting data for dissociation products:
Acid: Propionic acid is biodegradable in activated sludge, with 40.4% removal of an initial concentration of 500 mg/L after 24 hours and 95% removal of an intial concentration of 400 mg/L after 10 days (See Appendix B(1): 3.5)
Metal: NA
Reliability :
Reference :

3.7 BIOCONCENTRATION

Type :
Guideline/method :
Species :
Exposure period : at °C
Concentration :

BCF	:
Elimination	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

4.1 ACUTE TOXICITY TO FISH

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
LC0	:	
LC50	:	
LC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	For calcium dipropionate, the 96-h LC50 for the freshwater fish *Leuciscus idus* was reported to be >10,000 mg/L. For sodium propionate, the 24-h LC50 for *Lepomis macrochirus* was 5000 mg/L. **Supporting data for dissociation products:** **Acid:** For propionic acid, the 48-h LC50 for *Cyprinus carpio* was 72 mg/L and the 24-h LC50 for *Lepomis macrochirus* was 188 mg/L. (See Appendix B(1): 4.1) Reported 96-h LC50 values for propionic acid include 85.3 ppm (95% CI 73.0 – 99.7ppm) for *Lepomis macrochirus* and 67.1 ppm (95% CI: 61.6 – 73.2 ppm) for *Oncorhynchus mykiss.* (US EPA Office of Pesticide Programs Environmental Effects Database, cited in ECOTOX). **Metal:** For cobalt chloride, the 96-h LC50 was 333 mg Co/L for *Cyprinus carpio* and 1,406 mg Co/L for *Onchorynchus mykiss* (ECOTOX data base).
Reliability	:	
Reference	:	

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
EC0	:	
EC50	:	
EC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	

Result	:	
Remark	:	For calcium dipropionate, the 48-h EC50 for *Daphnia magna* was reported to be > 500 mg/L. **Supporting data for dissociation products:** **Acid:** For propionic acid, the 48-h EC50 for *Daphnia magna* was reported to be 50 mg/L. (See Appendix B(1): 4.2). Reported 48-h EC50 value for *Daphnia magna* for propionic acid was 22.7 ppm (95% CI: 21.0 – 24.6 ppm) [US EPA Office of Pesticide Programs Environmental Effects Database, cited in ECOTOX]. **Metal:** For cobalt chloride, the reported 48-h EC50 values for *Daphnia magna* range from 1.11 to 5.6 mg Co/L (ECOTOX data base).
Reliability	:	
Reference	:	

4.3 TOXICITY TO AQUATIC PLANTS (e.g., Algae)

Type	:	
Guideline/method	:	
Species	:	
Endpoint	:	
Exposure period	:	
NOEC	:	
LOEC	:	
EC0	:	
EC10	:	
EC50	:	
EC20	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	For calcium dipropionate, the 72-h EC50 for *Scenedesumus subspicatus* was reported to be > 500 mg/L. **Supporting data for dissociation products:** **Acid:** For propionic acid, the 72-h EC50 for *Scenedesmus subspicatus* was reported to be 43 - 45.8 mg/L (See Appendix B(1): 4.3). **Metal:** For cobalt chloride, the 96-h EC50 for *Chlorella vulgaris* was 0.522 mg/L (ECOTOX data base).
Reliability	:	
Reference	:	

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo :
Type :
Guideline/method :
Species :
Number of animals :
Males :
Females :
Doses :
Males :
Females :
Vehicle :
Route of administration :
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behavior :
Deg. product :
Deg products CAS#
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Propionic acid is a normal intermediary metabolite in animals and humans. Propionic acid occurs naturally in various foods including butter and cheese. (FASEB, 1979).
Metal: Absorption of cobalt in the digestive tract is influenced by the chemical form of the metal. The soluble form, cobalt chloride, is absorbed 13-34% in the gut of rats, but absorption in the gut may be increased in iron deficient individuals. The highest concentration of absorbed cobalt is in the liver and then the kidney. There is no accumulation of cobalt with age. Following oral exposure, cobalt is eliminated primarily in feces and secondarily in urine. For the more soluble forms of cobalt, e.g., cobalt chloride, 70 – 80% of the administered dose is eliminated in the feces. For absorbed cobalt, elimination is rapid primarily in the urine (Barceloux, D.G. (1999) Cobalt. *Clin. Tox.* 37(2):201-206). Elimination is biphasic or triphasic. The terminal phase involves a very small residual level of cobalt and has a half-life in years (ATSDR Sept 2001 Draft Toxicological Profile for Cobalt, U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry) (Subsequently listed as ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.1.1 ACUTE ORAL TOXICITY

Type :
Guideline/method :

Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Year	:	
LD50	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	For calcium dipropionate, oral LD50 values for the rat were 3920 – 4380 mg/kg and for the mouse were 2350 – 2900 mg/kg. For sodium propionate, the oral LD50 for the mouse was 5100 mg/kg. (See Appendix B(1): 5.1.1). **Supporting data for dissociation products:** **Acid:** For propionic acid, the following LC50 values for rats have been reported: 3470 mg/kg; 4290 mg/kg; 2600 mg/kg. (See Appendix B(1): 5.1.1). **Metal:** Acute oral toxicity values of the cobalt portion of the cobalt salts in this category are compared to simple cobalt salts such as cobalt chloride and cobalt sulfate. Reported LD50s of cobalt chloride to rats range from 42.4 to 190 mg $CoCl_2$/kg bw (equivalent to 19.1 to 85.5 mg Co/mg bw) (ATSDR Sept 2001 Draft). Toxicity of cobalt sulfate reported to be similar to the chloride with the oral LD50s for rats ranging from 123 to 161 mg/kg bw (equivalent to 55.4 to 72.5 mg Co/kg bw) (ATSDR Sept 2001 Draft). For the mouse, LD50 values were reported as 89.3 and 123 mg/kg for cobalt chloride and the cobalt sulfate, respectively, which are equivalent to 40.2 and 55.4 mg/kg bw when expressed as cobalt (ATSDR Sept 2001 Draft).
Reliability	:	
Reference	:	
Additional references	:	

5.1.2 ACUTE INHALATION TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	
Year	:	
GLP	:	
LC50	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	For calcium propionate and sodium propionate, the LC50 for inhalation of aerosol dust was reported to be > 5.4 mg/L. (See Appendix B(1): 5.1.2) **Supporting data for dissociation products:** **Acid:** Under similar conditions as reported above for calcium propionate and sodium propionate, the LC50 for propionic acid was >4.9 mg/L. (See

Appendix B(1): 5.1.2).
Metal: The acute LC50 for a 30-minute inhalation exposure in rats was 165 mg cobalt/m^3 as mixed cobalt oxides. (ATSDR, 1992, Toxicological Profile for Cobalt). In a 1 hour exposure to a dust aerosol of cobalt powder, the LC50 for rats was >10 mg/L (IUCLID, 2000).

Reliability :
Reference :

5.1.3 ACUTE DERMAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : For calcium propionate, the LD50 for dermal exposure for the rabbit was reported to be 500 mg/kg.
Supporting data for dissociation products:
Acid: For propionic acid, the LD50 for dermal exposure for the rabbit was reported to be 500 mg/kg (See Appendix B(1): 5.1.3).
Metal: Increased proliferation of lymphatic cells was seen in mice and guinea pigs dermally exposed to cobalt chloride, with LOAEL values ranging from 9.6 to 14.7 mg Co/kg/day. (ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.2.1 SKIN IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : Calcium priopionate and sodium propionate were found not irritating in the

		Draize skin irritation test with rabbits. (See Appendix B(1): 5.2.1). **Supporting data for dissociation products:** **Acid:** Propionic acid caused mild irritation to rabbits following 4 h closed contact of the skin with a 2.5% aqueous solution, mild to moderate irritation with 25% solution, and moderate to severe irritation and corrosion at concentrations of 40% and above. Propionic acid was a severe irritant to guinea pig skin. (See Appendix B(1): 5.2.1). **Metal:** Cobalt is reported to be irritating to the skin (IUCLID, 2000).
Reliability	:	
Reference	:	

5.2.2 EYE IRRITATION

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Concentration	:	
Dose	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
Classification	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Calcium propionate and sodium propionate were found not irritating in the Draize eye irritation test with rabbits. Propionic acid was irritating to rabbits (See Appendix B(1): 5.2.2)
Reliability	:	
Reference	:	

5.4 REPEATED DOSE TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatment	:	
Post exposure period	:	
Doses	:	
Control group	:	
NOAEL	:	
LOAEL	:	
Other	:	
Year	:	

GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Calcium propionate and sodium propionate, administered in feed over 7 weeks at 750 – 1200 mg/kg/day, did not affect weight gain in rats. In a 90-day feeding study, the NOAEL for calcium propionate was 166 mg/kg for male rats and 830 mg/kg for female rats. For a one-year exposure period, the oral NOAEL for sodium propionate in rats was 1320 mg/kg. **Supporting information for dissociation products:** **Acid:** Beagles fed propionic acid for 90 days exhibited lack of appetite at the highest dose (2000 mg/kg bw) but no other clinical, hematological or clinico-chemical effects. (See Appendix B(1): 5.4). Propionic acid in the diet (4% or 3320 mg/kg) of rats caused enhanced incorporation of methyl-H3-thymidine in the mucosa of the forestomach after 21 and 28 days of treatment, and macroscopic and histological lesions (general and nodular mucosal thickening) were observed in the forestomach after 27 days. This may reflect the response of the forestomach epithelium to changed pH (Rodrigues, C., Lok, E., Nera, E., Iverson, F., Page, D., Karpinski, K. and Clayson, D.B., 1986. Short-term effects of various phenols and acids on the Fischer 344 male rat forestomach epithelium, Toxicology 38:103-117). **Metal:** Repeated oral dosing of rats with cobalt chloride at levels ranging from 0.5 to 30.2 mg Co/kg/day (as cobalt chloride) for periods ranging from 12-16 days up to 7 months resulted in the following observations associated with LOAELs: reduced weight gain, increases in some organ weights (heart, liver and lungs); increased hematocrit, hemoglobin, and RBCs; renal tubular necrosis; and various changes on cardiac physiology (left ventricular hypertrophy, impaired ventricular function, and degeneration of myofibrils) (ATSDR Sept 2001 Draft). Cardiac effects were observed in rats at LOAEL's ranging from 8.4 to 12.4 mg Co/kg/day, for cobalt sulfate or cobalt chloride, with exposure periods of 3 weeks to 6 months (ATSDR Sept 2001 Draft).
Reliability	:	
Reference	:	

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	
Guideline/method	:	
System of testing	:	
Species	:	
Strain	:	
Test concentrations	:	
Cytotoxic concentr.	:	
Metabolic activation	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Calcium propionate was not mutagenic in a variety of assays. Calcium and sodium propionate were negative in the Ames test; calcium propionate caused a slight increase in the number of Chinese hamster lung cells but sodium propionate caused no chromosomal abberrations even at a higher concentration [Ishidate et al., 1984, as cited in Basler et al., 1987].

Supporting information for dissociation products:
Acid: Propionic acid was evaluated for genotoxic properties using the *E.coli* DNA repair assay, the SOS chromotest, the Salmonella/microsome mutagenicity test, the sister chromatid exchange test *in vitro* and the micronucleus test *in vivo.* All tests except the DNA repair assay yielded negative results. (Basler, A., von der Hude, W. And Scheutwinkel, M., 1987. Screening of the food additive propionic acid for genotoxic properties, Fd. Chem. Toxic. 25:287-290).
Metal: Cobalt compounds with a valence state of II, the form of cobalt released by dissociation of cobalt salts, are reported to be generally non-mutagenic in bacterial assays, but increased frequency of genetic conversions have been reported in yeast. Cobalt compounds with a valence state of III were weakly mutagenic in bacterial systems (ATSDR Sept 2001 Draft).

Reliability :
Reference :

5.6 GENETIC TOXICITY 'IN VIVO'

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Doses :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : Calcium dipropionate was not mutagenic in the cytogenetic assay and dominant lethal assay with rats, nor in the host-mediated assay with mice. No increase in chromosome abberations in the bone marrow cells of the rat were observed after dosing with sodium propionate (See Appendix B(1): 5.6). **Supporting information for dissociation products:**
Acid: Propionic acid was not gentoxic in the micronucleus test *in vivo.* (Basler, A., von der Hude, W. And Scheutwinkel, M., 1987. Screening of the food additive propionic acid for genotoxic properties, Fd. Chem. Toxic. 25:287-290).
Metal: Cobalt compounds, including salts, are observed to be genotoxic or mutagenic in mammalian systems. Cobalt compounds, including cobalt salts, are reported to be clastogenic in mammalian cells. Increased micronucleus formation was observed following *i.p.* injection of 12.4 and 22.3 mg Co/kg (as cobalt chloride), but not after injection of 6.19 mg Co/kg (as cobalt chloride) (NOEL) (ATSDR Sept 2001 Draft).

Reliability :
Reference :

5.8.2 DEVELOPMENTAL TOXICITY

Type :
Guideline/method :
Species :

Strain	:	
Sex	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatment	:	
Duration of test	:	
Doses	:	
Control group	:	
NOAEL maternal tox.	:	
NOAEL teratogen.	:	
Other	:	
Other	:	
Other	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	In developmental toxicity tests with various species, no maternal or teratogenic effects of calcium propionate were seen at the highest dose used, e.g. 300 mg/kg/day for mice and rats; 400 mg/kg/day for rabbits and golden hamsters. **Supporting information for dissociation products:** **Metal:** In a single developmental toxicity study with cobalt chloride exposure (5.4 or 21.8 mg Co/kg/day) from gestation day 14 to lactation day 21 the LOAEL was based on stunted pup growth. However, maternal toxicity was observed in conjunction with effects on the offspring. This growth effect was considered to be a secondary or indirect effect rather than a direct effect of cobalt on the fetus. No teratogenic effects were observed. Another study in rats provided a NOAEL of 24.8 mg Co/kg/day for cobalt chloride exposure from gestation days 6-15. No effects on fetal growth or survival in mice exposed to 81.7 mg Co/kg/day as cobalt chloride during gestation days 8-12 (ATSDR Sept 2001 Draft).
Reliability	:	
Reference	:	

5.8.3 TOXICITY TO REPRODUCTION

Type	:	
Guideline/method	:	
In vitro/in vivo	:	
Species	:	
Strain	:	
Sex	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatm.	:	
Duration of test	:	
Doses	:	
Control group	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	

Result	:	
Remark	:	**Supporting information for dissociation products:** **Metal:** Testicular degeneration and atrophy have been reported in rats exposed to 13.2 to 30.2 mg Co/kg/day as cobalt chloride for 2-3 months in the diet or drinking water. (ATSDR Sept 2001 Draft). Similar effects were seen in mice exposed to 23 to 43.4 mg Co/kg/day as cobalt chloride in drinking water for 10-13 weeks. In addition, reduced numbers of pregnant females and pups per litter, and reduced fertility, were observed in mice at 58.9 mg Co/kg/day. (ATSDR Sept 2001 Draft).
Reliability	:	
Reference	:	

6.0 OTHER INFORMATION

6.1 CARCINOGENICITY.

Supporting information for dissociation products:
Acid: Pre-neoplastic/pre-cancerous changes in rats fed 4% (2640 mg/kg) propionic acid were reported by Griem (1985). Hyperplasia, hyperplastic ulcers, papillomas and proliferation of the basal cells in the mucuosa of the forestomach were observed. Over the lifetime exposure, the high dose (4% propionic acid) resulted in 19/20 rats with dysplasia of glandular stomach mucosa while this effect was seen in 10/20 rats at the low dose (0.4%) and 5/20 control rats. However, Basler et al. (1987) concluded that propionic acid is not mutagenic and that genotoxic events are unlikely to be involved in the generation of these forestomach lesions. (See Appendix B(1): 5.7; also Basler, A., von der Hude, W. And Scheutwinkel, M., 1987. Screening of the food additive propionic acid for genotoxic properties, Fd. Chem. Toxic. 25:287-290).
Metal: The US National Toxicology Program does not recognize cobalt as a human carcinogen, but IARC has classified cobalt and cobalt compounds as possibly carcinogenic to humans (Class 2B) based on sufficient evidence that cobalt metal powder and cobaltous oxide are carcinogenic in animals (Barceloux 1999, ATSDR Sept 2001 Draft). "No studies were located regarding carcinogenic effects in animals after oral exposure to stable [non-radioactive] cobalt." (ATSDR Sept 2001 Draft).

1. General Information

ID 7646-79-9

Date January 31, 2005

1.0 SUBSTANCE INFORMATION

Generic Name	:	Cobalt chloride
Chemical Name	:	Cobaltous chloride
CAS Registry No.	:	7646-79-9
Component CAS Nos.	:	
EINECS No.	:	
Structural Formula	:	$CoCl_2$
Molecular Weight	:	129.84
Synonyms and Tradenames	:	Cobalt(II) chloride; Cobalt dichloride
References	:	ATSDR, 2001. Draft Toxicological Profile for Cobalt, U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry (ATSDR), September 2001. (This reference is subsequently listed in this document as ATSDR Sept 2001 Draft).

2.1 MELTING POINT

Type	:	
Guideline/method	:	
Value	:	735 °C
Decomposition	:	at °C
Sublimation	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Decomposes at 400 °C on long heating in air
Reliability	:	2 (reliable with restrictions): Source is well established data compendium.
Reference	:	O'Neil, M.J., Smith, A., Heckelman, P.E., and J.R. Obenchain (eds.). 2002. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Ed. Merck & Co., Inc., Whitehouse Station, NJ

2.2 BOILING POINT

Type	:	
Guideline/method	:	
Value	:	1,049 °C
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	2 (reliable with restrictions): Source is well established data compendium.
Reference	:	O'Neil, M.J., Smith, A., Heckelman, P.E., and J.R. Obenchain (eds.). 2002. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Ed. Merck & Co., Inc., Whitehouse Station, NJ

2.3 DENSITY

Type	:	
Guideline/method	:	
Value	:	3.367 at 25 °C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	2 (reliable with restrictions): Source is well established data compendium.
Reference	:	O'Neil, M.J., Smith, A., Heckelman, P.E., and J.R. Obenchain (eds.). 2002. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Ed. Merck & Co., Inc., Whitehouse Station, NJ

2.4 VAPOR PRESSURE

Type	:	
Guideline/method	:	
Value	:	hPa at °C
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

2.5 PARTITION COEFFICIENT

Type	:	
Guideline/method	:	
Partition coefficient	:	
Log Pow	:	at °C
pH value	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Not applicable – metal dissociates (ionizes) in water
Reliability	:	
Reference	:	

2.6.1 SOLUBILITY IN WATER

Type	:	
Guideline/method	:	
Value	:	450 g/L at 7 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
PKa	:	at °C
Description	:	
Stable	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	544 g/L in ethanol; 86 g/L in acetone
Reliability	:	2 (reliable with restrictions): Source is well established data compendium
Reference	:	Weast. R.C. (ed.). 1988-1989. Handbook of Chemistry and Physics. 69th Ed. CRC Press Inc., Boca Raton, FL., p. B-86.

2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	°C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.1.1 PHOTODEGRADATION

Type				
Guideline/method	:			
Light source	:			
Light spectrum	:			
Relative intensity	:	based on		
Spectrum of substance	:	lambda (max, >295nm)	:	
		epsilon (max)	:	
		epsilon (295)	:	
Conc. of substance	:		at	°C
DIRECT PHOTOLYSIS				
Halflife (t1/2)	:			
Degradation	:	% after		
Quantum yield	:			
INDIRECT PHOTOLYSIS				
Sensitizer	:			
Conc. of sensitizer	:			
Rate constant	:			
Degradation	:			
Deg. product	:			
Year	:			
GLP	:			
Test substance	:			
Deg. products CAS#	:			
Method	:			
Method detail	:			
Result	:			
Remark	:	Not applicable – metal does not degrade		
Reliability	:			
Reference	:			

3.2.1 MONITORING DATA

Type of measurement	:
Media	:
Concentration	:
Substance measured	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

3.3.1 TRANSPORT (FUGACITY)

Type	:	
Media	:	
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Year	:	
Test substance	:	
Method	:	

Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.5 BIODEGRADATION

Type	:	
Guideline/method	:	
Inoculum	:	
Concentration	:	related to related to
Contact time	:	
Degradation	:	(±) % after day(s)
Result	:	
Kinetic of test subst.	:	% (specify time and % degradation) % % % %
Control substance	:	
Kinetic	:	% %
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Not applicable – the metal will not degrade
Reliability	:	
Reference	:	

3.7 BIOCONCENTRATION

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	at °C
Concentration	:	
BCF	:	
Elimination	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

4.1 ACUTE TOXICITY TO FISH

Type	:	Acute
Guideline/method	:	Flow-through, freshwater
Species	:	Rainbow trout (*Onchorhynchus mykiss*)
Exposure period	:	96 hr
NOEC	:	
LC0	:	
LC50	:	1.41 mg Co/L (95% C.I. = 0.57 – 3.47 mg Co/L)
LC100	:	
Other	:	LC20 = 0.53 mg Co/L (95% C.I. = 0.24 – 1.20 mg Co/L)
Other	:	Incipient lethal level for 50% mortality (time independent) = 0.35 mg Co/L
Other	:	144-hr LC50 = 0.52 mg Co/L (95% C.I. = 0.29 – 0.95 mg Co/L)
Limit test	:	
Analytical monitoring	:	Yes (results based on measured concentrations)
Year	:	1998
GLP	:	No
Test substance	:	Cobalt chloride dihydrate ($CoCl_2 \cdot 2H_20$)
Method	:	
Method detail	:	Tests were conducted with trout fry in water with an alkalinity and hardness of approximately 25 mg $CaCO_3$/L. Exposure concentrations ranged from 0.125 to 2.0 mg Co/L. Exposures were continued for up to 14 days, with mortality assessed every 2 hr for the first 48 hr, and every 6 h thereafter.
Result	:	The onset of mortality was slow (48 hr or greater), generally not reaching a plateau for 200 hr or more.
Remark	:	Study data indicate that the rainbow trout is highly sensitive to the toxic effects of cobalt. For comparison, reported 96-h LC50 values for other fish species include 22.0 mg Co/L for the fathead mninnow (*Pimephales promelas*), 333 mg Co/L for the carp (*Cyprinus carpio*), and 275 mg Co/L for the mummichog (*Fundulus heteroclitus*) (U.S. EPA, ECOTOX data base, 2003). Available data suggest that toxicity to fish is reduced with increasing hardness up to a hardness of approximately 400 mg $CaCO_3$/L (Diamond, J. et al., 1992. Aquat. Toxicol., 22:163-180).
Reliability	:	2 (Reliable with restrictions): comparable to guideline study
Reference	:	Marr, J.C.A., J.A. Hansen, J.S. Meyer, D. Cacela, T. Podrabsky, J. Lipton, and H.L. Bergman. 1998. Toxicity of cobalt and copper to rainbow trout: application of a mechanistic model for predicting survival. Aquat. Toxicol., 43(4):225-238.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	Acute
Guideline/method	:	Static, freshwater
Species	:	*Daphnia magna* (water flea)
Exposure period	:	48 hr
NOEC	:	
EC0	:	
EC50	:	1.52 mg Co/L (95% C.I. = 1.01 - 2.28 mg Co/L)
EC100	:	
Other	:	24 hr LC50 = 2.11 mg Co/L (95% C.I. = 1.49 - 3.05 mg Co/L)
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	No
Year	:	1987
GLP	:	No

Test substance	:	Cobalt chloride hexahydrate ($CoCl_2 \cdot 6H_20$)
Method	:	American Public Health Association (APHA), 1976, Standard Methods for the Examination of Water and Wastewater.
Method detail	:	Tests were conducted in well water with a total hardness of 240 mg $CaCO_3$/L and a total alkalinity of 400 mg $CaCO_3$/L. Solutions were not renewed during the test. Daphnids were not fed during the test.
Result	:	
Remark	:	In an older study, the 48-hr LC50 for *Daphnia magna* has been reported as 5.5 mg Co/L (Cabejszek and Stasiak, 1960 as cited in the U.S. EPA ECOTOX database, 2003). The 48-hr LC50 for another daphnid, *Daphnia hyaline*, has been reported as 1.52 mg Co/L (Baudouin and Scoppa, 1974 as cited in the U.S. EPA ECOTOX database, 2003). Others have found 48-hr LC50 values for *Ceriodaphnia dubia* of 2.35, 4.60, and 4.20 mg Co/L for tests conducted with water hardness of 50, 200, and 400 mg $CaCO_3$/L, respectively (Diamond, J. et al., 1992. Aquat. Toxicol., 22:163-180).
Reliability	:	2 (Reliable with restrictions): comparable to guideline study
Reference	:	Khangarot, B.S., P.K. Ray, and H. Chandra. 1987. *Daphnia magna* as a model to assess heavy metal toxicity: comparative assessment with mouse system. Acta. Hydrochim. Hydrobiol., 15(4): 427-432.

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type	:	Algal growth assay
Guideline/method	:	Static, freshwater
Species	:	*Chlorella vulgaris* (green algae)
Endpoint	:	Population growth
Exposure period	:	96 hr
NOEC	:	
LOEC	:	
EC0	:	
EC10	:	
EC50	:	0.52 mg Co/L (95% C.I. = 0.48 – 0.56 mg Co/L)
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	No
Year	:	1993
GLP	:	
Test substance	:	Cobalt chloride
Method	:	
Method detail	:	Tests conducted in modified Bristol's medium (pH 6.5) with a 16:8 day/night photoperiod (280 foot candles). Cultures were incubated at 19°C ± 1°C. Results were based on experiments run in triplicate.
Result	:	Growth was 63.8% and 28.4% of controls at concentrations of 0.32 and 1.00 mg Co/L, respectively.
Remark	:	Other aquatic plants are much less sensitive to cobalt. The reported 96-h EC50 for *Spirulina platensis* (blue-green algae) is 23.8 mg Co/L (Sharma et al., 1987 as cited in the U.S. EPA ECOTOX database, 2003). The 7-d IC50 for *Lemna minor* (duckweed) is 16.9 mg Co/L (Dirilgen and Inel, 1994 as cited in the U.S. EPA ECOTOX database, 2003).
Reliability	:	2 (reliable with restrictions); comparable to guideline study
Reference	:	Rachlin, J.W. and A. Grosso. 1993. The growth response of the green alga *Chlorella vulgaris* to combined divalent cation exposure. Arch. Environ. Contam. Toxicol., 24: 16-20.

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:	
Type	:	
Guideline/method	:	
Species	:	
Number of animals	:	
Males	:	
Females	:	
Doses	:	
Males	:	
Females	:	
Vehicle	:	
Route of administration	:	
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1st.: 2nd.: 3rd.:
Toxic behavior	:	
Deg. product	:	
Deg. products CAS#	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Absorption of cobalt in the digestive tract is influenced by the chemical form of the metal, with increasing solubility resulting in increasing absorption (ATSDR Sept 2001 Draft). Approximately 13-34% of cobalt chloride, a soluble form, is absorbed in the gut of rats, but absorption in the gut may be increased in iron deficient individuals. Following oral exposure, cobalt is eliminated primarily in feces and secondarily in urine. For the more soluble forms of cobalt, e.g., cobalt chloride, 70 – 80% of the administered dose is eliminated in the feces. For absorbed cobalt, elimination is rapid primarily in the urine (Barceloux, D.G. 1999. Cobalt. Clin. Tox. 37:201-206). Elimination is biphasic or triphasic. The terminal phase involves a very small residual level of cobalt and has a half-life in years (ATSDR Sept 2001 Draft).
Reliability	:	
Reference	:	

5.1.1 ACUTE ORAL TOXICITY

Type	:	Oral
Guideline/Method	:	Not specified
Species	:	Rat
Strain	:	Wistar
Sex	:	Male and female
Number of animals	:	5 per sex per dose level
Vehicle	:	Distilled water
Doses	:	50, 600, 720, 864, and 1137 mg/kg

LD50	:	766 mg/kg as compound (hexahydrate); 95% C.I. = 677 – 867 mg/kg) 190 mg/kg as cobalt
Year	:	1982
GLP	:	No
Test substance	:	Cobalt(II) chloride hexahydrate ($CoCl_2 \cdot 6H_20$)
Method	:	Single dose administered by gastric incubation
Method detail	:	Mortality assessed after a 10-d observation period.
Result	:	
Remark	:	Reported LD50s of cobalt chloride to rats range from 42.4 to 190 mg Co/kg bw (ATSDR Sept 2001 Draft). Toxicity of cobalt sulfate is reported to be similar to that of the chloride with oral LD50s for rats ranging from 123 to 161 mg Co/kg bw (ATSDR Sept 2001 Draft). For the mouse, LD50 values are 89.3 and 123 mg Co/kg for cobalt chloride and cobalt sulfate, respectively (ATSDR Sept 2001 Draft).
Reliability	:	2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
Reference	:	Speijers, G.J.A., E.I. Krajnc, J.M. Berkvens, and M.J. van Logten. 1982. Acute oral toxicity of inorganic cobalt compounds in rats. Food Chem. Toxicol., 20:311-314.

5.1.2 ACUTE INHALATION TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	
LC50	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	No acute toxicity studies have been located for this compound.
Reliability	:	
Reference	:	

5.1.3 ACUTE DERMAL TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
LD50	:	
Year	:	
GLP	:	
Test substance	:	

Method	:	
Method detail	:	
Result	:	
Remark	:	Increased proliferation of lymphatic cells was seen in rats, mice and guinea pigs dermally exposed to cobalt chloride in DMSO once per day for 3 consecutive days, with LOAEL values ranging from 9.6 to 14.7 mg Co/kg/day (Ikarashi, Y., et al., 1992. Toxicology, 76:283-292). Stimulation indices of 3 or greater (indicative of a significant response by the authors), were reported for mice exposed to 1, 2.5 or 5% $CoCl_2$ (equivalent to 10.8, 27, or 54.1 mg Co/kg/day), rats exposed to 2.5 or 5% $CoCl_2$ (equivalent to 9.6 or 19.2 mg Co/kg/day), and guinea pigs exposed to 5% $CoCl_2$ (equivalent to 14.7 mg Co/kg/day).
Reliability	:	
Reference	:	

5.2.1 SKIN IRRITATION

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
Classification	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Dermatitis is a common result of dermal exposure to cobalt in humans and has been verified in a large number of studies (ATSDR Sept 2001 Draft). The dermatitis is probably caused by an allergic reaction to cobalt.
Reliability	:	
Reference	:	

5.2.2 EYE IRRITATION

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Concentration	:	
Dose	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
Classification	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	

Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

5.4 REPEATED DOSE TOXICITY

Type	:	Repeated dose
Guideline/method	:	Oral
Species	:	Rat
Strain	:	Not specified
Sex	:	Male
Number of animals	:	30
Route of admin.	:	Oral via stomach tube
Exposure period	:	150 to 210 days
Frequency of treatment	:	Five days per week
Post exposure period	:	0 to 30 days
Doses	:	4 or 10 mg Co/kg
Control group	:	Yes
NOAEL	:	
LOAEL	:	4 mg Co/kg (organ weights increased)
Other	:	
Year	:	1959
GLP	:	No
Test substance	:	Cobalt chloride
Method	:	
Method detail	:	The erythrocyte count, hemoglobin and hematocrit determinations were performed at frequent intervals for animals receiving 10 mg Co/kg. At study termination, all rats were sacrificed, organs examined and weighed, and sections made histological examination.
Result	:	The average weights of kidneys, livers, and spleens of the cobalt-treated groups were slightly heavier than the controls. Cobalt exposure at 10 mg/kg produced significant polycythemia. Histological examination of the kidneys revealed necrosis of the linings of the tubules in rats treated with 10 mg Co/kg, but not in those of the 4 mg Co/kg group. The effects was reversible, however, as examination of kidneys of rats autopsied 30 days after cobalt administration was discontinued showed no necrosis and were normal compared to the kidneys from control rats.
Remark	:	Results are highly consistent with those reported by others. Repeated oral dosing of rats with cobalt chloride at levels ranging from 0.5 to 30.2 mg Co/kg/day (as cobalt chloride) for periods ranging from 12-16 days up to 7 months resulted in the following observations associated with LOAELs: reduced weight gain, increases in some organ weights (heart, liver and lungs); increased hematocrit, hemoglobin, and red blood cells; renal tubular necrosis; and various changes on cardiac physiology (left ventricular hypertrophy, impaired ventricular function, and degeneration of myofibrils) (ATSDR Sept 2001 Draft). Cardiac effects were observed in rats at LOAEL's ranging from 8.4 to 12.4 mg Co/kg/day, for cobalt sulfate or cobalt chloride, with exposure periods of 3 weeks to 6 months (ATSDR Sept 2001 Draft).
Reliability	:	2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
Reference	:	Murdock, H.R. 1959. Studies on the pharmacology of cobalt chloride. J. Amer. Pharm. Assoc., 48:140-142.
Type	:	Repeated dose

Guideline/method	:	Not specified
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	Male
Number of animals	:	4
Route of admin.	:	Oral
Exposure period	:	8 weeks
Frequency of treatment	:	Daily
Post exposure period	:	None
Doses	:	2.5, 10, or 40 mg/kg (equivalent to 0.6, 2.5, or 10 mg Co/kg)
Control group	:	Yes
NOAEL	:	0.6 mg Co/kg
LOAEL	:	2.5 mg Co/kg (hemoglobin, red blood cell count)
Other	:	
Year	:	1947
GLP	:	No
Test substance	:	Cobalt chloride hexahydrate ($CoCl_2 \cdot 6H_20$)
Method	:	
Method detail	:	Cobalt was administered orally in a gelatin capsule (mixed in equal part of wheat flour and powdered sugar). Blood counts and hemoglobin determinations were made at the start of the test and at two week intervals.
Result	:	Hemoglobin content and numbers of erythrocytes were increased in rats receiving either 2.5 or 10 mg Co/kg/day, but not in those receiving 0.6 mg Co/kg/day.
Remarks	:	Other researchers have reported similar results in long-term studies with rats although many study details are lacking in the published report (Krasovskii, G.N. and S.A. Fridlyand. 1971. Hyg. Sanit., 26:277-279). They found that oral doses of 0.5 and 2.5 mg Co/kg six days per week for seven months stimulated hemopoiesis and decreased immunological reactivity (reduced the phagocytic index). Daily doses of 0.5 mg Co/kg and greater also produced mild to moderate increases in conditioned flexes. However, daily doses of 0.05 mg Co/kg had no effects on the indices investigated. Others have also reported the neurotoxic and behavior effects of cobalt on rats after chronic dietary exposures (Nation, J.R. et al., 1983. Neurobehav. Toxicol. Teratol., 5:9-15).
Reliability	:	2 (reliable with restrictions): Documentation was incomplete; however, the results are highly consistent with others in the scientific literature.
Reference	:	Stanley, A.J., H.C. Hopps, and A.M. Shideler. 1947. Cobalt polycythemia. II. Relative effects of oral and subcutaneous administration of cobaltous chloride. Proc. Soc. Exp. Biol. Med., 66:19-20.

5.5 GENETIC TOXICITY - MUTAGENICITY

Type	:	Mutagenicity
Guideline/method	:	Ames Assay
System of testing	:	Bacteria *in vitro*
Species	:	*Salmonella typhimurium* LT2
Strains	:	TA100
Test concentrations	:	10^{-4} to 10^{-1} M
Cytotoxic concentr.	:	10^{-2} M
Metabolic activation	:	No
Year	:	1981
GLP	:	No
Test substance	:	Cobalt chloride hexahydrate ($CoCl_2 \cdot 6H_20$)
Method	:	Ames, B.N., J. McCann, and E. Yamasaki. 1975. Mutat. Res., 31:347-364.
Method detail	:	

Result	:	Negative both above and below the cytotoxic concentration
Remark	:	Cobalt compounds with a valence state of II, the form of cobalt released by dissociation of cobalt chloride, are generally nonmutagenic in *in vitro* bacterial assays (ATSDR Sept 2001 Draft). For example, cobalt chloride was not mutagenic in plate incorporation and fluctuation assays with *Salmonella* TA strains or a *Escherichia coli* WP2 strain (Arlauskas, A., et al., 1985. Environ. Res., 36:379-388). However, a weak positive mutagenic response has been found in the rec assay with *Bacillus subtilis* at a concentration of 0.05 M (Kanematsu, N. et al., 1980. Mutat. Res., 77:109-116). A very weak positive response has also been found in Chinese hamster V79 cells, but only at a highly cytotoxic concentration (Miyaki, M. et al. 1979. Mutat. Res., 68: 259-263).
Reliability	:	2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
Reference	:	Tso, W-W. and W-P Fung. 1981. Mutagenicity of metallic cations. Toxicolog. Lett., 8:195-200.

Type	:	Mutagenicity
Guideline/method	:	Ames Assay
System of testing	:	Bacteria *in vitro*
Species	:	*Salmonella typhimurium* LT2
Strains	:	TA98, TA100, TA1537, and TA2637
Test concentrations	:	0.1 to 1,000 μM/plate
Cytotoxic conc.	:	Not specified
Metabolic activation	:	No
Year	:	1986
GLP	:	No
Test substance	:	Cobalt chloride
Method	:	Ames, B.N., J. McCann, and E. Yamasaki. 1975. Mutat. Res., 31:347-364.
Method detail	:	A modified Tris-HCl minimal medium with low phosphate content was used to prevent formation of insoluble metal phosphates in the test system.
Result	:	Negative
Remark	:	Although cobalt chloride alone did not produce mutants in this test system, it was mutagenic when it was added as a mixture with one of several heteroaromatic compounds (e.g., 4-aminoquinoline, 9-aminoacridine). The enhanced mutagenicity was attributed by the authors to the formation of weak to moderate complexes between these chemicals and the Co(II) cation, which may have enhanced transmembrane permeation or intercellular binding.
Reliability	:	2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
Reference	:	Ogawa, H.I., K. Sakata, T. Inouye, S. Jyosui, Y. Niyitani, K. Kamimoto, M. Morishita, S. Tsuruta, and Y. Kato. 1986. Combined mutagenicity of cobalt(II) salt and heteroaromatic compounds in *Salmonella typhimurium*. Mutat. Res., 172: 97-104.

5.6 GENETIC TOXICITY - CLASTOGENICITY

Type	:	Chromosomal aberrations in bone marrow cells
Guideline/method	:	*In vivo*
Species	:	Mouse (*Mus musculus*)
Strain	:	Swiss albino
Sex	:	Male
Route of admin.	:	Oral (single dose)
Exposure period	:	6, 12, 18, or 24 hr.
Dose	:	20, 40 , or 80 mg/kg b.w.
Year	:	1991
GLP	:	No
Test substance	:	Cobalt chloride hexahydrate ($CoCl_2 \cdot 6H_20$)
Method	:	Preston, R.J. et al., 1987. Mutat. Res., 189:157.
Method detail	:	Test compound was administered orally to five animals per dose group. Mice were 6-8 weeks old at that time. Colchicine (0.04%) was injected i.p. at 90 min prior to sacrifice. Bone marrow cells were removed form femurs by flushing with 0.8% sodium citrate. From each animal, 50 well-scattered metaphase plate were scored for chromosomal aberrations. Abnormalities were scored separately as total aberrations (with and without gaps) and as breaks per cell.
Result	:	Administration of cobalt chloride produced a concentration-dependent increase in total chromosomal aberrations.
Remark	:	Cobalt compounds, including soluble salts, are observed to be clastogenic (cause chromosomal aberrations) in a range of mammalian assay systems. For example, increased micronucleus formation was observed following i.p. injection of 12.4 and 22.3 mg Co/kg (as cobalt chloride), but not after injection of 6.19 mg Co/kg (NOEL) (ATSDR Sept 2001 Draft). There is evidence that soluble cobalt(II) cations exert a genotoxic activity in vitro and in vivo in experimental systems, but evidence in humans is lacking (Lison, D. et al., 2001. Occup. Environ. Med., 58: 619-625).
Reliability	:	2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
Reference	:	Palit, S., A. Sharma, and G. Talukder. 1991. Chromosomal aberrations induced by cobaltous chloride in mice in vivo. Biol. Trace Elem. Res., 29:139-145.

Type	:	Micronucleus Test
Guideline/method	:	In vivo
Species	:	Mouse
Strain	:	BALB/c AnNCRj
Sex	:	Male
Route of admin.	:	Intraperitoneally
Exposure period	:	30 hr
Doses	:	25, 50, or 90 mg Co/kg b.w.
Year	:	1993
GLP	:	No
Test substance	:	Cobalt chloride hexahydrate ($CoCl_2 \cdot 6H_20$)
Method	:	Von Ledbur, M. and W. Schmid. 1973. Mutat. Res., 19:109-117.
Method detail	:	Mice were injected once ip and sacrificed after 30 hr. Bone marrow smears were prepared and stained. The incidence of micronucleated polychromatic erythrocytes (MPCE) was determined in 1,000 cells. In addition, the ratio of polychromatic erythrocytes (P) to normochromatic erythrocytes (N) was determined in 2,000 erythrocytes.
Result	:	Treatment with cobalt induced a dose-dependent increase in the frequency of MPCE. The P/N ratio was significantly reduced ($P<0.05$) in mice dosed at 90 mg/kg b.w.

Remark	:	This study also included an *in vitro* micronucleus test with mouse bone marrow cells, both with and without metabolic activation with an S9 fraction. In contrast to the *in vivo* test, the *in vitro* test did not produce any significant changes in frequency of MPCE or the P/N ratio at dose levels of cobalt chloride hexahydrate up to 50 mg/L in the cell suspension.
Reliability	:	2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
Reference	:	Suzuki, Y., H. Shimizu, Y. Nagae, M. Fukumoto, H. Okonogi, and M. Kadokura. 1993. Micronucleus test and erythropoiesis: effect of cobalt on the induction of micronuclei by mutagens. Environ. Mol. Mutagen., 22:101-106.
Type	:	DNA damage in isolated human lymphocytes
Guideline/method	:	Alkaline Comet Assay (*in vitro*)
Species	:	Human
Strain	:	
Sex	:	Female
Route of admin.	:	In vitro
Exposure period	:	15 min
Doses	:	0.3, 0.6, 1.2, 1.5, 2.0, 2.5, 3.0, and 6.0 mg Co/L
Year	:	1998
GLP	:	No
Test substance	:	Cobalt chloride hexahydrate ($CoCl_2 \cdot 6H_20$)
Method	:	The alkaline comet assay performed using a modification of the method of Singh et al. 1988. Exp. Cell. Res., 175:184-191.
Method detail	:	Tests were conducted on lymphocytes taken from two healthy female donors. Cells were for 15 min exposed after 24 of stimulation by phytohaemagglutinin. After treatment, the cells were centrifuged for 10 min at 400 g. The supernatant was removed and the cell pellet was resuspended and processed for the alkaline comet assay (single cell electrophoresis assay). Fifty or 100 randomly selected slides were analyzed, with tail length, tail DNA, and tail movement recorded.
Result	:	There was considerable interexperimental and interdonor variability in data; however, at the highest dose level (6.0 mg Co/L) there was a statistically significant increase in tail movement in all experiments, indicating DNA damage (single strand breaks and alkali labile sites). Tail movement was also increased at lower doses, but did not show a clear dose-dependent trend.
Remark	:	Using human lymphocytes and macrophages ($P388D_1$ cells), an increase in sister chromatid exchanges (SCE) after exposure to cobalt chloride at 10^{-4} to 10^{-5} M has been also demonstrated (Andersen, O. 1983. Environ. Health Perspect., 47: 239-253). Others have also found that cobalt chloride increases DNA strand breaks in human diploid fibroblasts and Chinese hamster ovary cells after *in vitro* exposures, although only when determined by alkaline sediment sucrose velocity sedimentation and not when measured by nucleoid sedimentation or nick translation assays (Hamilton-Koch, W. et al., 1986. Chem.-Biol. Interactions, 59:17-28).
Reliability	:	2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
Reference	:	De Beck, M., D. Lison, and M. Kirsch-Volders. 1998. Evaluation of the in vitro direct and indirect genotoxic effects of cobalt compounds using the alkaline comet assay. Influence of interdonor and interexperimental variability. Carcinogenesis, 19:2021-2029.

5.8.2 DEVELOPMENTAL TOXICITY

Type	:	Developmental toxicity
Guideline/method	:	Not specified
Species	:	Rat
Strain	:	Wistar
Sex	:	Female
Route of admin.	:	Gastric intubation
Exposure period	:	Gestation day 14 through 21 days of lactation
Frequency of treatment	:	Daily
Duration of test	:	Through lactation day 21
Doses	:	12, 24, and 48 mg/kg b.w. (equivalent to 5.4, 10.8, or 21.8 mg Co/kg b.w.)
Control group	:	Yes
NOAEL maternal tox.	:	Not determined (no maternal data reported)
NOAEL teratogen.	:	Malformations not observed
Other	:	
Other	:	
Other	:	
Year	:	1985
GLP	:	No
Test substance	:	Cobalt chloride
Method	:	
Method detail	:	Cobalt chloride was administered to three groups of 15 pregnant rats from gestation day 14 through the 21st day of lactation. Pups were weighed and examined for signs of toxicity on days 1, 4, and 21 of lactation, and were sacrificed on day 21. Macroscopic examinations were made of the heart, lungs, spleen, liver, and kidneys following sacrifice. Clinical chemistry parameters were also measured.
Result	:	There was significant mortality of pups in the highest dose group and fewer litters produced at all dose levels. In addition, pups showed stunted growth (weight and length) at all dose levels. Relative weights of the liver (males and females) and spleen (females only) were reduced by cobalt exposure, but did not show a dose-related trend. Blood analysis and clinical chemistry showed no treatment related differences. No external malformations were observed in pups. Data from previous studies by the authors suggests that the upper two doses levels were maternally toxic, therefore, the results observed may have been indirectly due, at least in part, to effects on the mothers, rather than direct effects on the fetuses.
Remark	:	
Reliability	:	2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
Reference	:	Domingo, J.L., J.L. Paternain, J.M. Llobet, and J. Corbella. 1985. Effects of cobalt on postnatal development and late gestation in rats upon oral administration. Rev. Esp. Fisiol., 41:293-298.

Type	:	Teratogenicity
Guideline/method	:	Not specified
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	Female
Route of admin.	:	Oral gavage
Exposure period	:	Day 6 to 15 of gestation
Frequency of treatment	:	Daily
Duration of test	:	To day 20 of gestation
Doses	:	25, 50, or 100 mg/kg (equivalent to 6.2, 12.4, and 24.8 mg Co/kg b.w.)
Control group	:	Yes

NOAEL maternal tox.	:	Not determined (effects on weight gain seen at lowest dose)
NOAEL teratogen.	:	24.8 mg Co/kg b.w.
Other	:	NOAEL for maternal hematology was 12.4 mg Co/kg b.w.
Other	:	
Other	:	
Year	:	1998
GLP	:	
Test substance	:	Cobalt chloride hexahydrate ($CoCl_2 \cdot 6H_20$)
Method	:	
Method detail	:	Pregnant females (20 per group) were dosed daily with cobalt chloride hexahydrate in distilled water during gestation days 6 to 15. Maternal body weights were recorded on days 0, 6, 9, 12, 16, and 19 of gestation. Individual food consumption was recorded for the following intervals: days 0-6, 6-9, 9-12, 12-16 and 16-19. Detailed physical examinations for signs of toxicity were performed at the same time that weights were recorded. On day 20 of gestation, dams were weighed, then sacrificed. Blood samples were collected for hematological analyses. After exsanguinations, the uterine horns were opened, examinations made and the following recorded: number of corpora lutea, total implantations, number of live and dead fetuses number of resorptions, average fetus body weight, number of stunted fetuses, fetal body length, and fetal tail length. Fetuses were also fixed, stained and examined for skeletal abnormalities.
Result	:	Maternal effects included significant reductions in weight gain and food consumption, particularly at the 24.8 mg Co/kg dose level, although effects on weight gain were found at all dose levels. Hematological parameters (e.g., hematocrit, hemoglobin content) were significantly increased in the highest dose group. No treatment-related changes were observed in the number of corpora lutea, total implants, resorptions, number of live and dead fetuses per litter, fetal size parameters, or fetal sex distribution data. Increased incidences of stunted fetuses per litter (those under two-thirds of the average fetus body weight) were seen in the two highest dose groups; however, the increases were not statistically significant. Examination of fetuses for gross external abnormalities, skeletal malformations, and ossification variations produced negative findings, indicating that cobalt doses as high as 24.8 mg Co/kg do not produce teratogenicity or significant fetotoxicity in the rat.
Remark	:	A lack of teratogenicity in the golden hamster has also been reported (Ferm, V.H. 1972. Adv. Teratol., 6:51-75.
Reliability	:	2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
Reference	:	Paternain, J.L., J.L. Domingo, and J. Corbella. 1988. Developmental toxicity of cobalt in the rat. J. Toxicol. Environ. Health, 24:193-200.
Type	:	Developmental toxicity
Guideline/method	:	Chernoff/Kavlock developmental toxicity screen
Species	:	Mouse
Strain	:	ICR/SIM
Sex	:	Female
Route of admin.	:	Oral intubation
Exposure period	:	Gestation days 8 through 12
Frequency of treatment	:	Daily
Duration of test	:	Through postnatal day 3
Dose	:	180 mg/kg/day (equivalent to 81.7 mg Co/kg)
Control group	:	Yes
NOAEL maternal tox.	:	Not determined
NOAEL teratogen.	:	180 mg/kg/day (equivalent to 81.7 mg Co/kg)
Other	:	

Other	:	
Other	:	
Year	:	1986
GLP	:	
Test substance	:	Cobalt chloride
Method	:	Chernoff, N. and R.J. Kavlock. 1982. J. Toxicol. Environ. Health, 10:541-550.
Method detail	:	The screening test was carried out with a single minimally dose that was expected to result in significant maternal weight reduction, up to 10% mortality, or other clinical sings of overt toxicity. Treatment was by oral intubation on days 8 through 12 of gestation. Mice were allowed to deliver, and neonates examined, counted, and weighed on the day of birth (day 1) and day 3. Dead neonates were recovered from the nest and examined for abnormalities.
Result	:	The average maternal weight gain was significantly affected by cobalt treatment as desired in the protocol. Despite this, there was no effect of cobalt on litter size, percent survival of neonates on days 1-3, or average neonatal weight.
Remark	:	Results are in agreement with those seen in the rat, although another researcher has reported that injections of cobalt chloride to pregnant mice can lead to interference of skeletal ossification in fetuses (Wide, M. 1984. Environ. Res., 33:47-53).
Reliability	:	2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
Reference	:	Seidenberg, J.M. D.G. Anderson, and R.A. Becker. 1986. Validation of an in vivo developmental toxicity screen in the mouse. Teratog. Carcinog. Mutagen., 6:361-374.

5.8.3 TOXICITY TO REPRODUCTION

Type	:	Male reproduction
Guideline/method	:	Not specified
In vitro/in vivo	:	In vivo
Species	:	Mouse
Strain	:	CD-1
Sex	:	Male
Route of admin.	:	Drinking water
Exposure period	:	12 weeks (dose-response study); 13 weeks (time course study)
Frequency of treatment	:	Continuous
Duration of test	:	12 weeks (dose-response study); 33 weeks (time course study)
Doses	:	10, 200, or 400 ppm in the dose-response study (equivalent to a daily intake of 23.0, 42.0, or 72.1 mg Co/kg b.w.); 400 ppm in the time course study (equivalent to a daily intake of 58.9 mg Co/kg b.w.)
Control group	:	Yes
Year	:	1988
GLP	:	No
Test substance	:	Cobalt chloride hexahydrate ($CoCl_2 \cdot 6H_20$)
Method	:	
Method detail	:	In the dose-response study, males (5 per dose) were evaluated after 12 weeks of exposure for testicular weight, epididymal sperm concentration, sperm motility, sperm fertilizing ability (fertility), prostatic weight, seminal vesicle weight, and serum levels of testosterone. In the time course study, males (5 per dose and time point) were evaluated after 7, 9, 11, or 13 weeks of exposure for most of these same parameters. In addition, fertility of the males was evaluated at regular intervals up to 20 weeks after cessation of cobalt treatment in the drinking water.
Result	:	Cobalt exposure affected male reproductive parameters in a time- and

		dose-dependent manner. There was a significant decrease in testicular weight and epididymal sperm concentration after 11-13 weeks of exposure at all dose levels. Sperm motility and fertility were significantly depressed in the highest exposure groups. After cessation of exposure, some recovery was seen in fertility over time; however, indices remained significantly depressed through study termination (20 weeks after cessation). Parallel studies with acute cobalt chloride exposures (i.p injections of 200 μmoles/kg for 3 consecutive days) did not result in significant changes in male reproductive parameters, although transient affects on fertility were observed.
Remark	:	Histopathology studies of testes from mice treated with the same general exposure regimen as in this study (i.e., 400 ppm in drinking water for 13 weeks) showed a reproducible, sequential pattern of seminiferous tubule degeneration (Anderson, M.B. et al., 1992. Reprod. Toxicol., 6:41-50). Results of this study are highly consistent with others in which testicular degeneration and atrophy have been reported in rats exposed to 13.2 to 30.2 mg Co/kg/day as cobalt chloride for 2-3 months in the diet or drinking water (ATSDR Sept 2001 Draft).
Reliability	:	2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
Reference	:	Pedigo, N.G., W.J. George, and M.B. Anderson. 1988. Effects of acute and chronic exposure to cobalt on male reproduction in mice. Reprod. Toxicol., 2:45-53.
Type	:	Male reproduction
Guideline/method	:	Not specified
In vitro/in vivo	:	In vivo
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	Male
Route of admin.	:	Diet
Exposure period	:	98 d
Frequency of treatment	:	Continuous in diet
Duration of test	:	Up to 98 d
Doses	:	265 ppm in diet (equivalent to 20 mg Co/kg b.w. at test initiation)
Control group	:	Yes
Year	:	1985
GLP	:	No
Test substance	:	Cobalt chloride hexahydrate ($CoCl_2 \cdot 6H_20$)
Method	:	
Method detail	:	Three rats from the control and treatment groups were sacrificed on days 1, 2, 7, 14, 21, 28, 35, 42, 56, 63, 70, 84, and 98. Tissue specimens from the testes, cauda epididymus, and seminal vesicles were fixed and later examined.
Result	:	Dietary cobalt exposure induced consistent degenerative and necrotic lesions in the seminiferous tubules of rats. Cyanosis and engorgement of testicular vasculature on day 35 and thereafter was followed on day 70 by degenerative and necrotic changes in the germinal epithelium and Sertoli cells. Findings indicate that cobalt readily crosses the blood-testes barrier.
Remark	:	Results are consistent with those of Nation et al. (1983), who found significant testicular atrophy in rats exposed chronically to 20 mg Co/kg in the diet (Nation, J.R. et al., 1983. Neurobehav. Toxicol. Teratol., 5:9-15).
Reliability	:	2 (Reliable with restrictions): comparable to guideline study with adequate documentation.
Reference	:	Corrier, D.E., H.H. Mollenhauer, D.E. Clark, M.F. Hare, and M.H. Elissalde. 1985. Testicular degeneration and necrosis induced by dietary cobalt. Vet. Pathol., 22:610-616.

I U C L I D

D a t a s e t

Existing Chemical	Substance ID: 79-09-4
CAS No.	79-09-4
EINECS Name	propionic acid
EINECS No.	201-176-3
Molecular Formula	C3H6O2

Dataset created by: EUROPEAN COMMISSION - European Chemicals Bureau

This dossier is a compilation based on data reported by the European Chemicals Industry following 'Council Regulation (EEC) No. 793/93 on the Evaluation and Control of the Risks of Existing Substances'. All (non-confidential) information from the single datasets, submitted in the IUCLID/HEDSET format by individual companies, was integrated to create this document.

The data have not undergone any evaluation by the European Commission.

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1.0.1 OECD and Company Information

Name: BASF AG
Street: Karl–Bosch–Str
Town: 67056 Ludwigshafen
Country: Germany

Name: BP Chemicals Ltd.
Street: 76, Buckingham Palace Road
Town: SW1 WOSU London
Country: United Kingdom

Name: Celanese, N.V.
Street: Oude Maasweg 3197 KJ Botlek
Town: Rotterdam
Country: Netherlands

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Name: NEUBER GES.M.B.H.
Street: BRÜCKENGASSE 1
Town: 1060 WIEN
Country: Austria
Phone: 0222/599950
Telefax: 0222/5970200

1.0.2 Location of Production Site

–

1.0.3 Identity of Recipients

-

1.1 General Substance Information

Substance type: organic
Physical status: liquid

1.1.1 Spectra

-

1.2 Synonyms

Adofeed
Source: BASF AG Ludwigshafen

Antischim B
Source: BASF AG Ludwigshafen

Carboxyethane
Source: BASF AG Ludwigshafen

Ethanecarboxylic acid
Source: Celanese, N.V. Rotterdam
BASF AG Ludwigshafen

Ethylformic acid
Source: BASF AG Ludwigshafen

Luprosil
Source: BASF AG Ludwigshafen

Metacetonic acid
Source: BASF AG Ludwigshafen

Metacetonsäure, Methylessigsäure, Propansäure
Source: NEUBER GES.M.B.H. WIEN

Methylacetic acid
Source: Celanese, N.V. Rotterdam
BASF AG Ludwigshafen

MonoProp
Source: BASF AG Ludwigshafen

propanoic acid
Source: Celanese, N.V. Rotterdam
Eastman Chemical AG Zug
Eastman Chemical (Deutschland) GmbH Koln

Propanoic acid (9CI)
Source: BASF AG Ludwigshafen

Propcorn
Source: BASF AG Ludwigshafen

Propionic acid (6CI, 8CI)
Source: BASF AG Ludwigshafen

Propionsaeure
Source: BASF AG Ludwigshafen

Propkorn
Source: BASF AG Ludwigshafen

Prozoin
Source: BASF AG Ludwigshafen

Pseudoacetic acid
Source: BASF AG Ludwigshafen

1.3 Impurities

-

1.4 Additives

-

1.5 Quantity

Quantity 100 000 - 500 000 tonnes

1.6.1 Labelling

Labelling: as in Directive 67/548/EEC
Symbols: C
Nota: B
D
Specific limits: yes
R-Phrases: (34) Causes burns
S-Phrases: (1/2) Keep locked up and out of reach of children
(23) Do not breathe ...
(36) Wear suitable protective clothing
(45) In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)

1.6.2 Classification

Classification: as in Directive 67/548/EEC
Class of danger: corrosive
R-Phrases: (34) Causes burns

1.7 Use Pattern

Type: type
Category: Non dispersive use

Type: type
Category: Use in closed system

Type: type
Category: Wide dispersive use

Type: industrial
Category: Agricultural industry

Type: industrial
Category: Basic industry: basic chemicals

Type: industrial
Category: Chemical industry: used in synthesis

Type: industrial
Category: other: feed preservative

Type: industrial
Category: other

Type: use
Category: Food/foodstuff additives

Type: use
Category: Intermediates

Type: use
Category: other

1.7.1 Technology Production/Use

-

1.8 Occupational Exposure Limit Values

Type of limit: MAK (DE)
Limit value: 10 ml/m3
Short term expos.
Limit value: 20 ml/m3
Schedule: 5 minute(s)
Frequency: 8 times
Source: BASF AG Ludwigshafen

(1)

Type of limit: MAK (DE)
Limit value: 30 mg/m3
Source: BASF AG Ludwigshafen

(1)

Type of limit: OES (UK)
Limit value: 31 mg/m3
Remark: OES = 31 mg/m3, 8 hour TWA
Source: Eastman Chemical AG Zug
Eastman Chemical (Deutschland) GmbH Koln

(2)

Type of limit: OES (UK)
Limit value: 10 ml/m3
Short term expos.
Limit value: 15 ml/m3
Source: BP Chemicals Ltd. London

Type of limit: TLV (US)
Limit value: 30 mg/m3
Source: Celanese, N.V. Rotterdam

Type of limit: TLV (US)
Limit value: 31 mg/m3
Source: Eastman Chemical AG Zug
Eastman Chemical (Deutschland) GmbH Koln

(3)

Type of limit: TLV (US)
Limit value: 30 mg/m3
Source: BASF AG Ludwigshafen

(4)

Type of limit: TLV (US)
Limit value:
Remark: Limit value: 10 ppm
Source: BASF AG Ludwigshafen

(4)

Type of limit: TLV (US)
Limit value: 30 mg/m3
Source: BASF AG Ludwigshafen

(4)

1.9 Source of Exposure

Remark: The recommended method of disposal is by incineration under controlled conditions.
Source: Eastman Chemical AG Zug
Eastman Chemical (Deutschland) GmbH Koln

1.10.1 Recommendations/Precautionary Measures

-

1.10.2 Emergency Measures

-

1.11 Packaging

-

1.12 Possib. of Rendering Subst. Harmless

-

1.13 Statements Concerning Waste

-

1.14.1 Water Pollution

Classified by: KBwS (DE)
Labelled by: KBwS (DE)
Class of danger: 1 (weakly water polluting)
Source: BASF AG Ludwigshafen

Classified by: KBwS (DE)
Labelled by:
Class of danger: 1 (weakly water polluting)
Source: BASF AG Ludwigshafen

1.14.2 Major Accident Hazards

Legislation: Stoerfallverordnung (DE)
Substance listed: no
Source: BASF AG Ludwigshafen

(5)

1.14.3 Air Pollution

Classified by: TA-Luft (DE)
Labelled by: TA-Luft (DE)
Number: 3.1.7 (organic substances)
Class of danger: II
Source: BASF AG Ludwigshafen

1.15 Additional Remarks

Remark: Propionic acid is shipped either in bulk or in polyethylene drums. The bulk shipments are in tank trucks, rail tank cars, or rail tank containers. Our warehouses check that the transporters have the necessary papers and equipment available in case of an emergency.
Source: Eastman Chemical AG Zug
Eastman Chemical (Deutschland) GmbH Koln

1.16 Last Literature Search

-

1.17 Reviews

-

1.18 Listings e.g. Chemical Inventories

-

2.1 Melting Point

Value: ca. -20 degree C
Source: BASF AG Ludwigshafen
(6)

Value: = 22.4 degree C
Source: BASF AG Ludwigshafen
(7)

2.2 Boiling Point

Value: = 140.7 - 141.6 degree C
Source: BASF AG Ludwigshafen
(6)

2.3 Density

Type: density
Value: = .992 g/cm3 at 20 degree C
Source: BASF AG Ludwigshafen
(6)

2.3.1 Granulometry

-

2.4 Vapour Pressure

Value: = 5 hPa at 20 degree C
Source: BASF AG Ludwigshafen
(6)

2.5 Partition Coefficient

log Pow: = .25
Method:
Year:
Source: BASF AG Ludwigshafen
(6) (8)

log Pow: = .278
Method: other (calculated): Inkrementenmethode von Rekker mit Computerprogramm der Firma CompuDrug Ltd.
Year:
Source: BASF AG Ludwigshafen
(9)

log Pow: = .33
Method:
Year:
Source: BASF AG Ludwigshafen
(10)

2.6.1 Water Solubility

Value: at 20 degree C
Qualitative: miscible
pH: 2.5 at 100 g/l and 20 degree C
Source: BASF AG Ludwigshafen
(6)

2.6.2 Surface Tension

-

2.7 Flash Point

Value: = 50 degree C
Type: closed cup
Method: other: DIN 51 755
Year:
Source: BASF AG Ludwigshafen
(6)

Value: = 52.3 degree C
Type: other: Pensky-Martens closed cup
Method:
Year:
GLP: yes
Source: BASF AG Ludwigshafen
(11)

Value: = 54 degree C
Type: other: Tag open cup
Method: other: ASTM D56
Year:
GLP: no
Source: BASF AG Ludwigshafen
(12)

2.8 Auto Flammability

Value: = 466 degree C
Method: other: ASTM D2155
GLP: no
Source: BASF AG Ludwigshafen
(12)

Value: = 485 degree C
Method: other: DIN 51 794
Source: BASF AG Ludwigshafen

(6)

2.9 Flammability

Result:
Remark:
Type: lower flammable limit
Value: 3.04 % at 64 dgree C
Method: ASTM E681
GLP: no

type: upper flammable limit
Value: 14.9 % at 118 degree C
Method: ASTM E681
GLP: no

Type: lower temperature limit
Value: 48 degree C
Method: ASTM E1232
GLP: no

Type: upper temperature limit
Value: 81 degree C
Method: ASTM E1232
GLP: no

Source: BASF AG Ludwigshafen

(12)

2.10 Explosive Properties

Result:
Remark: Explosionsgrenzen in Luft: 2,1-12,0 Vol.%
Source: BASF AG Ludwigshafen

(6)

Result:
Remark:
Type: Differential Thermal Analysis
Value: no exothermiv activity to 138 degree C
Method: ASTM E537
GLP: no

Source: BASF AG Ludwigshafen

(13)

Result:
Remark:
Type: Differential Thermal Analysis
Value: no exothermiv activity to 138 degree C
Method: ASTM E537
GLP: no

Source: BASF AG Ludwigshafen

(13)

2.11 Oxidizing Properties

–

2.12 Additional Remarks

Remark: Gefaehrliche Reaktionen: Exotherme Reaktion mit starken Basen.
Source: BASF AG Ludwigshafen

(6)

Remark: Viscosity
Type: Average Viscosity (n=3)
Value: less than 5 centipoises at 25 degree C +/–1 degree C
Method: Modification of rotational viscometer method described in OECD, Section 4, No. 114

Corrosion Characteristics
Method: Modifications of methods described in ASTM G31–72
Comment: The average corrosion rate of zinc foil when exposed to aqueous suspensions of test material for 7 days was determined to be 1mm/year, with a standard deviation of 0.0. There was no significant change in temperature (> 2 degree C), evolution of gases, noxious fumes, flames, or splattering observed when aqueous supsensions of test material were placed in contact witg solid reactant (zinc foil).
Source: BASF AG Ludwigshafen

(14)

Remark: Combustible, otherwise stable.
Source: BASF AG Ludwigshafen

(15)

Remark: Viscosity
Type: Average Viscosity (n=3)
Value: less than 5 centipoises at 25 degree C +/–1 degree C
Method: Modification of rotational viscometer method described in OECD, Section 4, No. 114

Corrosion Characteristics
Method: Modifications of methods described in ASTM G31–72
Comment: The average corrosion rate of zinc foil when exposed to aqueous suspensions of test material for 7 days was determined to be 1mm/year, with a standard deviation of 0.0. There was no significant change in temperature (> 2 degree C), evolution of gases, noxious fumes, flames, or splattering observed when aqueous supsensions of test material were placed in contact witg solid reactant (zinc foil).
Source: BASF AG Ludwigshafen

(14)

Remark: Combustible, otherwise stable.
Source: BASF AG Ludwigshafen

(15)

3.1.1 Photodegradation

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 500000 molecule/cm3
Degradation: = 50 % after 13.2 day
Method:
Year: **GLP:**
Test substance:
Remark: Rate Constant: 1.6 (+/- 0.5)*10^-12, bzw. 1.22 (+/-0.12)* 10^-12 cm^3/molecule*sec bei 298 K
Source: BASF AG Ludwigshafen
(16) (17)

Type: water
INDIRECT PHOTOLYSIS
Sensitizer: OH
Method:
Year: **GLP:**
Test substance:
Remark: Rate Constant: 0.79*10^9 l/mol*sec (rel. to ethanol: k= 1.85*10^9 l/mol*sec)
Source: BASF AG Ludwigshafen
(18)

Type: water
INDIRECT PHOTOLYSIS
Sensitizer: OH
Degradation: = 50 % after 4.7 year
Method: other (calculated)
Year: **GLP:**
Test substance:
Remark: Rate Constant: 0.47*10^9 l/mol*sec
Source: BASF AG Ludwigshafen
Test condition: room temperature; literature value for OH-radical concentration in water: 1*10^-17 mol/l; pH 9
(19)

3.1.2 Stability in Water

Type:
Method: other
Year: **GLP:**
Test substance:
Remark: no data are available
Source: BASF AG Ludwigshafen

3.1.3 Stability in Soil

Type: other **Radiolabel:**
Concentration:
Cation exch. capac.
Microbial biomass:
Method:
Year: **GLP:**
Test substance:
Remark: no data are available
Source: BASF AG Ludwigshafen

3.2 Monitoring Data (Environment)

Type of measurement: other
Medium: other: water
Remark: Propionic acid was detected in (with GC): Ohio 0.01–0.7 ug/l; Little Miami 0.4–0.5 ug/l; Tannes Creek 0.8 ug/l.
Source: BASF AG Ludwigshafen

(20)

Type of measurement: other
Medium: air
Remark: Propionic acid was found in Delft, Terschelling and Vlaadingen (Netherlands) in air (with GC): 0.15 ppm (mean); 2.0 ppm (max.)
Source: BASF AG Ludwigshafen

(21)

3.3.1 Transport between Environmental Compartments

Type: volatility
Media:
Method:
Year:
Remark: Henry’s Law Constant of 4.15*10^–7 atm*m^3/mol at 25 deg C
Source: BASF AG Ludwigshafen

(22)

3.3.2 Distribution

Media: other
Method:
Year:
Remark: no data are available
Source: BASF AG Ludwigshafen

3.4 Mode of Degradation in Actual Use

Remark: no data are available
Source: BASF AG Ludwigshafen

3.5 Biodegradation

Type: aerobic
Inoculum:
Degradation: = 69.1 % after 5 day
Method: other: Sea Water Dilution Method (BOD of THOD)
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen
Test condition: Test concentration: 5 ppm

(23)

Type: aerobic
Inoculum:
Degradation: = 78.1 % after 5 day
Method: other: Standard Dilution Method (BOD of THOD)
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen
Test condition: Test concentration: 5 ppm

(23)

Type: aerobic
Inoculum: activated sludge
Concentration: 400 mg/l
Degradation: ca. 95 % after 10 day
Method: other: Standversuch (TOC)
Year: **GLP:**
Test substance:
Remark: Gut eliminierbar, biologisch abbaubar.
lag-Phase: 1 d; Beginn der Plateauphase: nach 3 d
Source: BASF AG Ludwigshafen

(24)

Type: aerobic
Inoculum: other: activated sludge, municipal
Concentration: 500 mg/l related to Test substance
Degradation: = 40.4 % after 24 hour(s)
Method: other: Warburg Test (Respirometer); BOD of THOD
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen

(25)

Type: anaerobic
Inoculum: other: enriched methane cultures
Degradation: = 100 %
Method: other: Hungate Serum Bottle Technique
Year: **GLP:**
Test substance:
Remark: 100% degradation after 2 d lag; removal rate 90 mg/l per day
Source: BASF AG Ludwigshafen
Test condition: 50 ml Inoculum; 100 mg acetate; 25 mg test compound (500 mg/l); 6 injections of test compound

(26)

3.6 BOD5, COD or BOD5/COD Ratio

Method: other: Biochemical Oxygen Demand Method 405.1, U.S.EPA (EPA-600/4-79-020, March, 1979)

C O D

Method: other: Chemical Oxygen Demand Method 410.1, U.S.EPA (EPA-600/4-79-020, March, 1979)
COD: = 1420 mg/g substance

Remark: THOD: 1.51 g oxygen/g; BOD5: 0.77 oxygen/g; BOD5: 0.92 oxygen/g; COD: 1.42 oxygen/g
Source: BASF AG Ludwigshafen

(27)

3.7 Bioaccumulation

Species: other
Exposure period:
Concentration:
BCF:
Elimination:
Method:
Year: **GLP:**
Test substance:
Remark: no data are available
Source: BASF AG Ludwigshafen

3.8 Additional Remarks

-

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no
NOEC: = 5000
LC0: = 5000
LC50: > 10000
LC100: > 10000
Method: other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische, DIN 38412 Teil 15
Year: 1982 **GLP:** no
Test substance: other TS
Remark: 10000mg/l: lethality 2/10 after 96H
5000mg/l: no lethality
No toxic symptoms detectable.
Source: BASF AG Ludwigshafen
Test substance: Lupronilsalz (Calciumpropionat)

(28)

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no
NOEC: = 5000
LC0: = 5000
LC50: > 10000
LC100: > 10000
Method: other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische, DIN 38412 Teil 15
Year: 1982 **GLP:** no
Test substance: other TS
Remark: 10000mg/l: lethality 2/10 after 96H
5000mg/l: no lethality
No toxic symptoms detectable.
Source: BASF AG Ludwigshafen
Test substance: Lupronilsalz (Calciumpropionat)

(29)

Type: static
Species: Pimephales promelas (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: µg/l **Analytical monitoring:**
LC50: >= 1000
Method: other: see remarks
Year: **GLP:** no
Test substance: other TS
Remark: Highest concentration tested. pH adjusted upward.
Test method: Eastman Kodak Company, Health and Environment Laboratories Protocol according to Ewell, W.S, Gorsuch, J.W., Kringle, R.O, Robillard, K.A., and Spiegal, R.C. (Simultaneous Evaluation of the Acute Effects of Chemicals on Seven Species, Environ.Toxicol.Chem. 5,831-840, 1986). Similar to OECD Guideline 203.
Source: BASF AG Ludwigshafen
Test substance: Propionic acid

(30)

Type:
Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50: = 72
Method:
Year: **GLP:**
Test substance:
Remark: LC50 24h: 95mg/l.
Japanese article with abstract and figures in english.
Source: BASF AG Ludwigshafen

(31) (32)

Type:
Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50: = 188
Method:
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen

(33) (34) (35)

Type:
Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50: = 188
Method:
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen

(31) (36) (35)

Type:
Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50: = 5000
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(35)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Exposure period: 96 hour(s)
Unit: **Analytical monitoring:**
Method: other: Static test
Year: **GLP:**
Test substance:
Remark: EC50(96h)= 320 ul/l
Source: BASF AG Ludwigshafen
Test condition: pH adjusted upward
Test method: Eastman Kodak Company, Health and Environment Laboratories Protocol according to Ewell,W.S. et al., (Simultaneous Evaluation of the Acute Effects of Chemicals on Seven Species, Environ. Toxicol. Chem.5, 831–840, 1986

(27)

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:**
TLm : = 130
Method:
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen

(37)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
TLm : = 50
Method:
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen

(38)

Species: Gammarus pulex (Crustacea)
Exposure period:
Unit: mg/l **Analytical monitoring:**
Method:
Year: **GLP:**
Test substance:
Remark: perturbation level =6000 mg/l.
Source: BASF AG Ludwigshafen
(37)

Species: other aquatic mollusc: Helisoma trivolvis
Exposure period: 96 hour(s)
Unit: **Analytical monitoring:**
Method: other: Static test
Year: **GLP:** no
Test substance:
Remark: EC50(96h) >1000 ul/l (highest concentration tested)
Source: BASF AG Ludwigshafen
Test condition: Test method: Eastman Kodak Company, Health and Environment Laboratories Protocol according to Ewell,W.S. et al., (Simultaneous Evaluation of the Acute Effects of Chemicals on Seven Species, Environ. Toxicol. Chem.5, 831–840, 1986
(27)

Species: other aquatic worm: Dugesia tigrina
Exposure period: 96 hour(s)
Unit: **Analytical monitoring:**
Method: other: Static test
Year: **GLP:** no
Test substance:
Remark: EC50(96h) >1000 ul/l (highest concentration tested)
Source: BASF AG Ludwigshafen
Test condition: Test method: Eastman Kodak Company, Health and Environment Laboratories Protocol according to Ewell,W.S. et al., (Simultaneous Evaluation of the Acute Effects of Chemicals on Seven Species, Environ. Toxicol. Chem.5, 831–840, 1986
(27)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Chlorella pyrenoidosa (Algae)
Endpoint:
Exposure period:
Unit: mg/l **Analytical monitoring:**
toxisch : = 250
Method:
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen
(37)

Species: Scenedesmus subspicatus (Algae)
Endpoint:
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:**
EC50: = 45.8
EC20 : = 33.5
Method: other: Scenedesmus-Zellvermehrungs-Hemmtest, DIN 38412 Teil 9, Bestimmung der Hemmwirkung von Wasserinhaltsstoffen auf Gruenalgen
Year: **GLP:**
Test substance:
Remark: EC90(72h)=62.3 mg/l.
Source: BASF AG Ludwigshafen

(39)

Species: Scenedesmus subspicatus (Algae)
Endpoint:
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:**
EC50: = 43
EC20 : = 12
Method: other: Scenedesmus-Zellvermehrungs-Hemmtest, DIN 38412 Teil 9, Bestimmung der Hemmwirkung von Wasserinhaltsstoffen auf Gruenalgen
Year: **GLP:**
Test substance:
Remark: EC90(96h)=79 mg/l.
Source: BASF AG Ludwigshafen

(39)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type:
Species: activated sludge
Exposure period:
Unit: **Analytical monitoring:**
Method:
Year: **GLP:**
Test substance:
Remark: Bei sachgemaesser Einleitung (Neutralisation) in adaptierte biologische Klaeranlagen sind keine Stoerungen der Abbauaktivitaet von Belebtschlamm zu erwarten.
Source: BASF AG Ludwigshafen

(40)

Type:
Species: Paramaecium caudatum (Protozoa)
Exposure period:
Unit: mg/l **Analytical monitoring:**
Method:
Year: **GLP:**
Test substance:
Remark: Perturbation level: 8000 mg/l
Source: BASF AG Ludwigshafen

(41)

Type:
Species: Pseudomonas putida (Bacteria)
Exposure period: 17 hour(s)
Unit: mg/l **Analytical monitoring:**
EC10: = 44.6
EC50: = 59.6
EC90 : = 74.5
Method: other: Pseudomonas–Zellvermehrungs–Hemmtest, DIN 38412 Teil 8, zum Gelbdruck verabschiedet, Bestimmung der Hemmwirkung von Wasserinhaltsstoffen auf Bakterien
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen

(39)

Type:
Species: Pseudomonas putida (Bacteria)
Exposure period:
Unit: mg/l **Analytical monitoring:**
TGK : = 200
Method: other: Zellvermehrungshemmtest
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen

(42)

Type:
Species: other protozoa: Vorticella campanula
Exposure period:
Unit: mg/l **Analytical monitoring:**
Method:
Year: **GLP:**
Test substance:
Remark: Perturbation level: 4000 mg/l
Source: BASF AG Ludwigshafen

(41)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

Species: Salmo gairdneri (Fish, estuary, fresh water)
Endpoint:
Exposure period:
Unit: **Analytical monitoring:**
Method: other: BASF Test
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Remark: The treatment of about 9 month old rainbow trouts (60 animals per group, both sexes) with 0,5%; 1% and 1,5% propionic acid in pellet–feed for 7 weeks caused a dose–dependent loss of body– weight up to 23,1% in the high dose group in comparison to untreated control.
The histopathology of 5 animals out of each group revealed a more pronounced expression of viscerale granulomas with increasing concentration, but large interindividuel variations. The viscerale granuloma syndrom in combination with nephrocalcinoses is reported to be of polyfactorial etiology.
Source: BASF AG Ludwigshafen

(43)

Species: Salmo gairdneri (Fish, estuary, fresh water)
Endpoint:
Exposure period:
Unit: **Analytical monitoring:**
Method: other: BASF Test
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Remark: The treatment of about 9 month old rainbow trouts (60 animals per group, both sexes) with 0,5%; 1% and 1,5% propionic acid in pellet–feed for 7 weeks caused a dose–dependent loss of body– weight up to 23,1% in the high dose group in comparison to untreated control.
The histopathology of 5 animals out of each group revealed a more pronounced expression of viscerale granulomas with increasing concentration, but large interindividuel variations. The viscerale granuloma syndrom in combination with nephrocalcinoses is reported to be of polyfactorial etiology.
Source: BASF AG Ludwigshafen

(44)

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Species: other
Endpoint:
Exposure period:
Unit: **Analytical monitoring:**
Method:
Year: **GLP:**
Test substance:
Remark: no data are available
Source: BASF AG Ludwigshafen

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Soil Dwelling Organisms

Type: other
Species:
Endpoint:
Exposure period:
Unit:
Method:
Year: **GLP:**
Test substance:
Remark: no data are available
Source: BASF AG Ludwigshafen

4.6.2 Toxicity to Terrestrial Plants

Species: other terrestrial plant: Lolium perenne, Raphanus sativus, Lactuca sativa
Endpoint:
Expos. period: 7 day
Unit:
Method: other
Year: **GLP:** no
Test substance:
Remark: EC0(7d) =10 ul/l, all species
Germination effects
Source: BASF AG Ludwigshafen
Test condition: Test method: Eastman Kodak Company, Health and Environment Laboratories Protocol according to Gorsuch,J.W. et al. (Chemical Effects on the Germination and Early Growth of Terrestrial Plants, Plants for Toxicity Assessment, ASTM STP 1091, 49–58, 1990

(27)

Species: other terrestrial plant: Tagetes patula, Raphanus sativus, Lactuca sativa, Zea mays
Endpoint:
Expos. period: 7 day
Unit:
Method: other
Year: **GLP:** no
Test substance:
Remark: Early growth effects
EC0(7d) =100 ul/l, all species
Source: BASF AG Ludwigshafen
Test condition: Test method: Eastman Kodak Company, Health and Environment Laboratories Protocol according to Gorsuch,J.W. et al. (Chemical Effects on the Germination and Early Growth of Terrestrial Plants, Plants for Toxicity Assessment, ASTM STP 1091, 49–58, 1990

(27)

4.6.3 Toxicity to other Non–Mamm. Terrestrial Species

Species: other
Endpoint:
Expos. period:
Unit:
Method:
Year: **GLP:**
Test substance:
Remark: no data are available
Source: BASF AG Ludwigshafen

4.7 Biological Effects Monitoring

Remark: no data are available
Source: BASF AG Ludwigshafen

4.8 Biotransformation and Kinetics

Type: other
Remark: no data are available
Source: BASF AG Ludwigshafen

4.9 Additional Remarks

Remark: Aedes aegyptii (insect, larva: 2nd–3rd instar): LC50(4h)= 800 mg/l or 0.08% v/v; static test; dist. water; 22–24 deg C
Source: BASF AG Ludwigshafen

(45)

Remark: Culex pipens (insect): LC50(48h) >1000 mg/l; static test
Source: BASF AG Ludwigshafen

(38)

Remark: Culex pipens (insect): LC50(48h) >1000 mg/l; static test
Source: BASF AG Ludwigshafen

(38)

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 3470 mg/kg bw
Method: other: BASF-Test
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: apathy or restlessness, dyspnoea, partly cyanosis and accumulation of liquid in abdomen
Source: BASF AG Ludwigshafen

(46)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 4290 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: no further information
Source: BASF AG Ludwigshafen

(47) (48) (49) (50)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: > 400 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: 1%aqueous solution.
Source: BASF AG Ludwigshafen

(47) (51)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 5160 mg/kg bw
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate

(47) (52) (48)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 2600 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen

(53)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: 3920 – 4380 mg/kg bw
Method:
Year: **GLP:**
Test substance: other TS
Remark: LD50 male rats: 4280 or 4380 mg/kg
LD50 female rats: 3920 or 4040 mg/kg
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate

(54)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: ca. 6400 mg/kg bw
Method: other: BASF-Test
Year: **GLP:** no
Test substance: other TS
Remark: Symptoms: dyspnoea, apathy, abdominal position, piloerection Pathology: adhesion of stomach wall and liver
Source: BASF AG Ludwigshafen
Test substance: Calciumpropionat

(55)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: ca. 6500 mg/kg bw
Method: other: BASF–Test
Year: **GLP:** no
Test substance: other TS
Remark: Symptoms: dyspnoes, apathy; pathology without findings.
Source: BASF AG Ludwigshafen
Test substance: Calciumpropionat

(56)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 3470 mg/kg bw
Method: other: BASF–Test
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Remark: apathy or restlessness, dyspnoea, partly cyanosis and accumulation of liquid in abdomen
Source: BASF AG Ludwigshafen

(57)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 4290 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: no further information
Source: BASF AG Ludwigshafen

(58) (48) (59) (50)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: > 400 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: 1%aqueous solution.
Source: BASF AG Ludwigshafen
(58) (60)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 5160 mg/kg bw
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate
(58) (52) (48)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 2600 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen
(61)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: ca. 6400 mg/kg bw
Method: other: BASF-Test
Year: **GLP:** no
Test substance: other TS
Remark: Symptoms: dyspnoea, apathy, abdominal position, piloerection Pathology: adhesion of stomach wall and liver
Source: BASF AG Ludwigshafen
Test substance: Calciumpropionat
(62)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: ca. 6500 mg/kg bw
Method: other: BASF–Test
Year: **GLP:** no
Test substance: other TS
Remark: Symptoms: dyspnoes, apathy; pathology without findings.
Source: BASF AG Ludwigshafen
Test substance: Calciumpropionat

(63)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 835 – 1090 mg/kg bw
Method: other
Year: **GLP:** no data
Test substance: other TS: no data
Source: BASF AG Ludwigshafen
Reliability: (3) invalid

(64)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Value: = 5100 mg/kg bw
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(47) (52) (48)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Value: 2350 – 2900 mg/kg bw
Method:
Year: **GLP:**
Test substance: other TS
Remark: LD50 male mice: 2350 or 2600 mg/kg
LD50 female mice: 2400 or 2900 mg/kg
Another value of 3340 mg/kg is cited from unidentifiable literature.

Source: BASF AG Ludwigshafen
Test substance: Calcium propionate
(54)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Value: = 5100 mg/kg bw
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(58) (52) (48)

Type: LD50
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Value: ca. 695 mg/kg bw
Method: other: BASF-Test
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: symptoms: lack of appetite, at doses above LD50 dyspnoea, atonia and staggering.
Source: BASF AG Ludwigshafen
(65)

Type: LD50
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Value: ca. 695 mg/kg bw
Method: other: BASF-Test
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: symptoms: lack of appetite, at doses above LD50 dyspnoea, atonia and staggering.
Source: BASF AG Ludwigshafen
(66)

5.1.2 Acute Inhalation Toxicity

Type: LC50
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 1 hour(s)
Value: > 19.7 mg/l
Method: other: BASF-Test
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: vapor-exposure, LC50 > 4,9 mg/l/4h (converted with Habers-rule) irritation of respiratory system, corneal opacities
Source: BASF AG Ludwigshafen

(67)

Type: LC50
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 4 hour(s)
Value: > 5.4 mg/l
Method: other: BASF-Test
Year: **GLP:** no
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Calciumpropionate, dust aerosol

(68)

Type: LC50
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 4 hour(s)
Value: > 5.4 mg/l
Method: other: BASF-Test
Year: **GLP:** no
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodiumpropionate, dust aerosol;

(69)

Type: LC50
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 4 hour(s)
Value: > 4.9 mg/l
Method: other: BASF Test
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Remark: vapor–exposure, (converted with Habers–rule) irritation of respiratory system, corneal opacities
Source: BASF AG Ludwigshafen

(67)

Type: LC50
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 4 hour(s)
Value: > 5.4 mg/l
Method: other: BASF–Test
Year: **GLP:** no
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Calciumpropionate, dust aerosol

(70)

Type: LC50
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 4 hour(s)
Value: > 5.4 mg/l
Method: other: BASF–Test
Year: **GLP:** no
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodiumpropionate, dust aerosol;

(71)

Type: other: IRT
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 8 hour(s)
Value:
Method:
Year: **GLP:**
Test substance:
Remark: No mortality after 8 h exposure to an atmosphere enriched or saturated at 20 degree C. (0/6 rats)
Source: BASF AG Ludwigshafen
(49) (50)

Type: other: IRT
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 7 hour(s)
Value:
Method: other: in Anlehnung an die von H.F. Smith et al: Am.Ind.Hyg.Ass.J. 23, 95–107 (1962) beschriebene Methode durchgefuehrt
Year: 1962 **GLP:** no
Test substance: other TS
Remark: mortality 0/12 rats after 7 hours
Source: BASF AG Ludwigshafen
Test substance: Luprosil Salz (Zusammensetzung 75 % Propionsaeure und 20 % Calcium)
(72)

Type: other: IRT
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 8 hour(s)
Value:
Method:
Year: **GLP:**
Test substance:
Remark: No mortality after 8 h exposure to an atmosphere enriched or saturated at 20 degree C. (0/6 rats)
Source: BASF AG Ludwigshafen
(59) (50)

Type: other: IRT
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 7 hour(s)
Value:
Method: other: in Anlehnung an die von H.F. Smith et al: Am.Ind.Hyg.Ass.J. 23, 95-107 (1962) beschriebene Methode durchgefuehrt
Year: 1962 **GLP:** no
Test substance: other TS
Remark: mortality 0/12 rats after 7 hours
Source: BASF AG Ludwigshafen
Test substance: Luprosil Salz (Zusammensetzung 75 % Propionsaeure und 20 % Calcium)

(73)

Type:
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time:
Value:
Method:
Year: **GLP:**
Test substance:
Remark: Acute inhalation studies with 5000, 2000, 800, 100 and 23mg/m3 propionic acid yielded irritant effects in the upper 3 concentrations and no effects at 100 and 23 mg/m3. Obviously no mortality occured. The somewhat confuse description of systemic effects is not useable.
Source: BASF AG Ludwigshafen

(74)

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Value: = 500 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: no further information
Source: BASF AG Ludwigshafen

(48) (49) (50)

Type: LD50
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Value: = 500 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: no further information
Source: BASF AG Ludwigshafen
(48) (59) (50)

Type: LD50
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Value: = 501 – 794 mg/kg bw
Method: other
Year: **GLP:** no data
Test substance: other TS: no data
Source: BASF AG Ludwigshafen
Reliability: (3) invalid
(64)

Type: LD50
Species: guinea pig
Sex:
Number of Animals:
Vehicle:
Value: 4.96 – 9.93 mg/kg bw
Method: other: see remarks
Year: **GLP:** no
Test substance: other TS
Remark: Test predates codification of GLPs.
Test method: Eastman Kodak Company, Health, Safety and Human Factors Laboratory Protocol. Doses of 2.5, 5, or 10ml/kg were applied to the depilated abdomen of guinea pigs under an occlusive wrap for 24 hours. One guinea pig was used at each dose level.
(d=0.9933)
Source: BASF AG Ludwigshafen
Test substance: Propionic acid
(75)

Type: LD50
Species: guinea pig
Sex:
Number of Animals:
Vehicle:
Value: 4960 – 9930 mg/kg bw
Method: other: see remarks
Year: **GLP:** no
Test substance: other TS
Remark: Test predates codification of GLPs.
Test method: Eastman Kodak Company, Health, Safety and Human Factors Laboratory Protocol. Doses of 2.5, 5, or 10ml/kg were applied to the depilated abdomen of guinea pigs under an occlusive wrap for 24 hours. One guinea pig was used at each dose level.
(d=0.9933)
Source: BASF AG Ludwigshafen
Test substance: Propionic acid

(75)

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value: 200 – 400 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: 1% aqueous solution.
Source: BASF AG Ludwigshafen

(51)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value: 200 – 400 mg/kg bw
Method: other: see remarks
Year: **GLP:** no
Test substance: other TS
Remark: Tests predate codification of GLPs.
Test method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. The test material was administered as a 1% aqueous solution to five animals at dose levels ranging from 25 to 400 mg/kg body weight. One rat was used at each dose level. Rats were observed for 14 days; no necropsies were conducted.

Test result: The approximative intraperitoneal LD50 was between 200 and 400 mg/kg. Weakness and ataxia were observed in dosed animals.
Source: BASF AG Ludwigshafen
Test substance: Propionic acid

(76)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value: 200 – 400 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: 1% aqueous solution.
Source: BASF AG Ludwigshafen

(60)

Type:
Species: cat
Sex:
Number of Animals:
Vehicle:
Route of admin.: s.c.
Value: 1000 mg/kg bw
Method:
Year: **GLP:**
Test substance: other TS
Remark: Sleep
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(77)

Type:
Species: cat
Sex:
Number of Animals:
Vehicle:
Route of admin.: s.c.
Value: 1000 mg/kg bw
Method:
Year: **GLP:**
Test substance: other TS
Remark: Sleep
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(78)

Type:
Species: dog
Sex:
Number of Animals:
Vehicle:
Route of admin.: s.c.
Value: 925 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: Total dose 14,8 g. 1,05 g propionic acid excreted in urine. No abnormalities detected.
Source: BASF AG Ludwigshafen

(77)

Type:
Species: dog
Sex:
Number of Animals:
Vehicle:
Route of admin.: s.c.
Value: 925 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: Total dose 14,8 g. 1,05 g propionic acid excreted in urine. No abnormalities detected.
Source: BASF AG Ludwigshafen

(78)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.v.
Value: = 625 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: 10 % aqueous solution
Source: BASF AG Ludwigshafen

(79)

Type:
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.v.
Value: 1320 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: Lethal dose.
Source: BASF AG Ludwigshafen

(77)

Type:
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.v.
Value: 2200 mg/kg bw
Method:
Year: **GLP:**
Test substance: other TS
Remark: Sedation or narcosis for about 1h, afterwards no abnormalities
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(77)

Type:
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.v.
Value: 1320 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: Lethal dose.
Source: BASF AG Ludwigshafen

(78)

Type:
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.v.
Value: 2200 mg/kg bw
Method:
Year: **GLP:**
Test substance: other TS
Remark: Sedation or narcosis for about 1h, afterwards no abnormalities
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(78)

Type:
Species: dog
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.v.
Value: 570 mg/kg bw
Method:
Year: **GLP:**
Test substance: other TS
Remark: dullness, narcosis, vomiting
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(77)

Type:
Species: dog
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.v.
Value: 570 mg/kg bw
Method:
Year: **GLP:**
Test substance: other TS
Remark: dullness, narcosis, vomiting
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(78)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: corrosive
EC classificat.:
Method: other: BASF-Test
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Necrosis after exposure periods of 5 and 15 minutes but not after 1 minute.
Source: BASF AG Ludwigshafen

(80)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: corrosive
EC classificat.:
Method: other: DOT Methode were conducted in accordance with 19 CFR, Chapter I, Sec, 173.40 as amendment in Federal Register, Vol. 37, No. 57, March 23, 1972.
Year: 1972 **GLP:**
Test substance:
Remark: DOT-Method, 4h occlusive application to intact and abraded skin
Source: BASF AG Ludwigshafen

(81)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: 15% solution of propionic acid in water, not corrosive
Source: BASF AG Ludwigshafen

(82)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: Irritant, grade 6 of 10
Source: BASF AG Ludwigshafen

(48) (83) (84)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: Local damage may occur to skin on contact with concentrated solutions of propionic acid.
Source: BASF AG Ludwigshafen

(51)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: not irritating
EC classificat.:
Method: Draize Test
Year: 1973 **GLP:** no
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Calciumpropionate feed grade, sodiumpropionate

(85)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: irritating
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: Mild skin irritation was seen following 4 h closed contact of the skin with a 2.5 % aqueous solution, mild to moderate irritation occured with 25 % solutions, while moderate to severe irritation and corrosion were seen at concentrations of 40 % and above.
Source: BASF AG Ludwigshafen

(86)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: corrosive
EC classificat.:
Method: other: BASF-Test
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Necrosis after exposure periods of 5 and 15 minutes but not after 1 minute.
Source: BASF AG Ludwigshafen

(87)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: Irritant, grade 6 of 10
Source: BASF AG Ludwigshafen

(48) (59) (50)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: Local damage may occur to skin on contact with concentrated solutions of propionic acid.
Source: BASF AG Ludwigshafen

(60)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: not irritating
EC classificat.:
Method: Draize Test
Year: 1973 **GLP:** no
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Calciumpropionate feed grade, sodiumpropionate

(73)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: corrosive
EC classificat.: corrosive (causes burns)
Method: other
Year: **GLP:** no data
Test substance: other TS: no data
Result: Corrosive within 4 hours
Source: BASF AG Ludwigshafen
Test condition: Exposure time: 4 and 24 hours
Test substance (0.5 ml) was applied undiluted.
Reliability: (3) invalid

(64)

Species: guinea pig
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: irritating
EC classificat.:
Method: other: see remarks
Year: **GLP:** no
Test substance: other TS
Remark: Test predates codification of GLPs.
Test method: Eastman Kodak Company, Health, Safety and Human Factors Laboratory Protocol. Doses of 2.5, 5, or 10 ml/kg were applied to the depilated abdomen of guinea pigs under an occlusive wrap for 24 hours. One guinea pig was used at each dose level.
Test result: The test material was determined to be a severe irritant to guinea pig skin under the conditions of the test.
Source: BASF AG Ludwigshafen
Test substance: Propionic acid

(75)

Species: mammal
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance: other TS
Remark: species: dog and cat, irritation
depending on pH of solution: alkaline pH (8,4) irritant (like bicarbonate), neutral pH not irritant.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(88)

5.2.2 Eye Irritation

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: not irritating
EC classificat.:
Method:
Year: **GLP:**
Test substance: other TS
Remark: Sodium propionate, 20% solution, no description of method.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(88)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: Irritant, grade 9 of 10
Source: BASF AG Ludwigshafen

(48) (83) (50)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: not irritating
EC classificat.:
Method: Draize Test
Year: 1973 **GLP:** no
Test substance: other TS
Remark: Calciumpropionate feed grade, sodiumpropionate
Source: BASF AG Ludwigshafen
Test substance: Calciumpropionat

(85)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: Irritant, grade 9 of 10
Source: BASF AG Ludwigshafen

(48) (59) (50)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: not irritating
EC classificat.:
Method: Draize Test
Year: 1973 **GLP:** no
Test substance: other TS
Remark: Calciumpropionate feed grade, sodiumpropionate
Source: BASF AG Ludwigshafen
Test substance: Calciumpropionat

(73)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: corrosive
EC classificat.: risk of serious damage to eyes
Method: other
Year: **GLP:** no data
Test substance: other TS: no data
Source: BASF AG Ludwigshafen
Test condition: 0.1 ml were applied undiluted; exposure time: 1 min, 24 hrs; 14 days: ulceration
Reliability: (3) invalid

(64)

Species: rat
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: In a 4 h inhalation study atmospheric concentrations of around 5 mg/l propionic acid produced slight eye irritation during, and several hours after exposure.
Source: BASF AG Ludwigshafen

(89)

5.3 Sensitization

Type: Guinea pig maximization test
Species: guinea pig
Number of Animals:
Vehicle:
Result: not sensitizing
Classification:
Method: other: according to the method described by Magnusson and Kligmann "Allergie contact dermatitis in the guinea pig" Ed. Ch.C. Thomas, Springfield, Illinois, USA (1970)
Year: 1970 **GLP:** no
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Calcium– and sodiumpropionate

(90)

5.4 Repeated Dose Toxicity

Species: rat **Sex:** male
Strain: Wistar
Route of admin.: inhalation
Exposure period: 3-4 weeks
Frequency of treatment: "continuous exposure"
Post. obs. period:
Doses: 23 and 100 mg/m3
Control Group:
Method:
Year: **GLP:**
Test substance:
Remark: Due to major deficiencies in presentation of the data the study is considered to be not valid.
Result: Changes in lung tissue, bronchitis, peribronchitis, desquamation. The confuse presentation of further systemic effects is not usable.
Source: BASF AG Ludwigshafen

(74)

Species: rat **Sex:**
Strain: Wistar
Route of admin.: inhalation
Exposure period: 3-month
Frequency of treatment:
Post. obs. period:
Doses: 0,017; 0,17; 1,7 mg/m3
Control Group: yes
NOAEL: 1700 mg/l
Method:
Year: **GLP:**
Test substance:
Remark: Due to major deficiencies in presentation of the data the study is considered to be not valid.
Result: No morphological changes.
The clinical findings are undistinguishable confused with acute and subacute (?) studies.
Source: BASF AG Ludwigshafen

(74)

Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of admin.: oral feed
Exposure period: 90 days
Frequency of treatment: daily
Post. obs. period: 42 days, 10 rats per sex of control, 6200 and 50000ppm groups
Doses: 6200, 12500, 25000, 50000ppm (=517;1042;2083;4167mg/kg b.w.)
Control Group: yes, concurrent no treatment
NOAEL: 6200 ppm
Method: other: BASF-Test
Year: **GLP:** no
Test substance: other TS
Result: 20 rats per sex and dosage, 10 rats per sex and dosage for post- exposure-observation-period
50000ppm: feed intake and body weight gain of male animals reduced, no other clinical, hematological or clinicochemical effects, single slight deviations of absolute and relative organ weights without pathological significance, no macroscopic findings, proliferation-acanthosis and retention-hyperceratosis of forestomach mucosa. Reversibility in post-exposure-observation-period. 25000 and 12500ppm: dose-dependent occurance of forestomach- lesions as in the high dosage group, no significant other effects.
Source: BASF AG Ludwigshafen
Test substance: Propionsaeure technisch

(47) (91)

Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of admin.: oral feed
Exposure period: 28 days
Frequency of treatment: daily
Post. obs. period:
Doses: 10000, 20000, 50000ppm
Control Group: yes, concurrent no treatment
Method: other: BASF-Test
Year: **GLP:** no
Test substance: other TS
Result: 10 rats per sex and dosage group. Substance intake approx. 800, 1500 and 3900 mg/kg b.w. (Calc. from feed consumption). 50000 ppm: decrease in weight gain of the male animals, no other clinical, hematological or clinicochemical effects, decrease in absolute liverweight of male animals, no change in relative organweights, histologically detected proliferation-acanthosis and retention-hyperceratosis of the forestomach mucosa. 20000 and 10000 ppm: dose-dependent occurence of mucosal lesions of forestomach, no other symptoms.
Source: BASF AG Ludwigshafen

(47) (92)

Species: rat **Sex:** male
Strain: Sprague–Dawley
Route of admin.: oral feed
Exposure period: 30 days
Frequency of treatment: daily
Post. obs. period:
Doses: 4% (=40000ppm)
Control Group: yes, concurrent no treatment
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 – 1.4
Remark: Study was performed in order to assess the onset of lesions in the forestomach.
Result: 5 rats per sacrifice, sacrifices on days 2,4,7,10,14,22 and 30. Mean substance intake 3370mg/kg b.w. (calculated from feed intake).
No treatment related clinical findings. Pathology restricted to the forestomach. Macroscopic lesions from day ten onward, prominent limiting ridge and visible mucosal alterations. Histopathology: From day 2 onward acanthosis and hyperkeratosis, from day 14 basal cell hyperplasia. Ulcer in 1 rat and polyplike lesions in 3 animals after 22 and 30 days.
Source: BASF AG Ludwigshafen

(93)

Species: rat **Sex:**
Strain:
Route of admin.: oral feed
Exposure period: 3–4 weeks
Frequency of treatment:
Post. obs. period:
Doses: 1 and 3% (10000 and 30000ppm = 830 and 2490mg/kg)
Control Group: yes, concurrent no treatment
Method:
Year: **GLP:**
Test substance: other TS
Result: The application of 1% sodium or calcium propionate in feed for 4 weeks or of 3% of the substances for 3 weeks did not reduce weight gain in comparison to the control animals. No other parameters determined.
Source: BASF AG Ludwigshafen
Test substance: Sodium and Calcium propionate

(94)

Species: rat **Sex:** male
Strain: Fischer 344
Route of admin.: oral feed
Exposure period: 9, 15, 21, 27 days
Frequency of treatment: daily
Post. obs. period:
Doses: 4% (40000ppm = 3320mg/kg)
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Result: The incorporation of Methyl–H3–Thymidine into the mucosa of the forestomach was not influenced after 9 and 15 days but was enhanced after 21 and 28 days of treatment. Macroscopic and histologic lesions (general and nodular mucosal thickening) were observed in the forestomach after 27 days.
Source: BASF AG Ludwigshafen

(95)

Species: rat **Sex:** male/female
Strain: other: albino, mongrels
Route of admin.: oral feed
Exposure period: 110 days
Frequency of treatment: daily
Post. obs. period:
Doses: about 5% (50000ppm = 3300mg/kg)
Control Group:
Method:
Year: **GLP:**
Test substance:
Result: 5 rats.
No systemic toxicity.
1/5 early death. 3/4 umbilicate or warty lesions of forestomach mucosa, 1/4 no abnormalities. Hyperkeratosis and hyperplasia of forestomach mucosa. No lesions in the glandular stomach. Similar effects after treatment with butyric acid (even more effective) and valeric acid.
Source: BASF AG Ludwigshafen

(47) (96)

Species: rat **Sex:** female
Strain: other: Wistar (SLC)
Route of admin.: oral feed
Exposure period: 1 year
Frequency of treatment: daily
Post. obs. period:
Doses: 2% (20000ppm = 1320mg/kg), calculated total intake 185g/animal
Control Group: yes, concurrent no treatment
NOAEL: 2 %
Method:
Year: **GLP:**
Test substance: other TS
Remark: Japanes article with tables and abstracts in english.
Result: Very slight retardation of growth rate (b.w. at the end of the study 290g versa 299g in control). No hematological, clinicochemical or urinalytic changes. No changes in organ weights. Histopathology: different spontaneous findings without substance relation, thereof 2 mammary tumours and 1 myxoma of the uterus. These findings are considered to be not substance related because in a test group fed simultaniously with 2% sodium propionate and 5% sorbic acid no such changes occured.
(40 animals per group)
Source: BASF AG Ludwigshafen
Test substance: sodium propionate

(47) (97)

Species: rat **Sex:** male/female
Strain: Wistar
Route of admin.: oral feed
Exposure period: 1 year
Frequency of treatment: daily
Post. obs. period:
Doses: The animals were maintained on a feed consisting in 75% bread which was baked under addition of the 50 fold amount of 4 bread additives and bleached flour. One of the additives was 5% sodium propionate.
Control Group: yes
Method:
Year: **GLP:**
Test substance: other TS
Result: The animals were maintained on a feed consisting in 75% bread which was baked under addition of the 50 fold amount of 4 bread additives and bleached flour. One of the additives was 5% sodium propionate.
Interim sacrifices were performed and a number of organs were examined histologically. No clinical nor pathological effects were observed. Therefore the authors conclude that neither the single substances nor their mixture cause toxic effects. The complex mixture of substances and conduct of the study make it difficult to judge on the real effect, if at all for single substances.
Source: BASF AG Ludwigshafen

Test substance: Sodium propionate, 27 animals per sex (47) (51) (98) (48)

Species: rat **Sex:** male
Strain: Wistar
Route of admin.: oral feed
Exposure period: 32 weeks
Frequency of treatment: daily
Post. obs. period:
Doses: The animals were maintained on a feed consisting in 75% of a bakiing mixture for bread which contained the 50 fold amount of 4 bread additives and bleached flour. One of the additives was 5% sodium propionate.
Control Group: yes
Method:
Year: **GLP:**
Test substance: other TS
Result: The animals were maintained on a feed consisting in 75% of a baking mixture for bread which contained the 50 fold amount of 4 bread additives and bleached flour. One of the additives was 5% sodium propionate.
Groups fed with diets containing 5% propionate show a reduction in body weight gain but no substance related histopathological effects were observed. The study was furthermore complicated by infections in different testgroups. The complex mixture of substances and conduct of the study make it difficult to judge on the real effect, if at all for single substances.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate, 30 animals (47) (99)

Species: rat **Sex:** male/female
Strain: Wistar
Route of admin.: oral feed
Exposure period: f 4 weeks, m 8 weeks
Frequency of treatment: daily
Post. obs. period: 1 group m 8 weeks
Doses: 4% (40000ppm = 3320mg/kg KGW)
Control Group: yes
Method:
Year: **GLP:**
Test substance: other TS
Result: Wistar Han/BGA, 5 animals/sex
Clinical examination and organ weights without abnormalities. Forestomach 4 week exposure: hyperkeratosis and hyperplasie of l limiting ridge, isolated ulcerations in 4/5 animals. Forestomach 8 week exposure: more pronounced lesions in number and expression.
Reversibility of changes in 8 week post exposure observation period.
Similar effects produced by 4 and 6% acetic acid or 4% capronic acid.

Source: BASF AG Ludwigshafen
(100) (101)

Species: rat **Sex:** male
Strain: Wistar
Route of admin.: oral feed
Exposure period: 4 weeks
Frequency of treatment: daily
Post. obs. period:
Doses: 4% (40000ppm = 3320mg/kg KGW)
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Result: Clinical examination and organ weights without abnormalities. Forestomach : limiting ridge slightly thickend in 3/5, mucosa macroscopically unchanged. Histology: hyperkeratosis of mucosa, hyperplasia of basal cells at the limiting ridge in 1/5. In general obviously slighter forestomach-changes as compared to the acid. Similar effects produced by 4% Sodium acetate.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate, Wistar Han/BGA, 5 animals
(100) (102)

Species: rat **Sex:** male/female
Strain: Wistar
Route of admin.: oral feed
Exposure period: f 4 weeks, m 8 weeks
Frequency of treatment: daily
Post. obs. period:
Doses: 4% (40000ppm = 3320mg/kg KGW)
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Result: Reduction of feed consumption, body weight gain and abs. organ weights.
Forestomach: 4 week exposure: Slight thickening of limiting ridge. Hyperkeratosis and hyperplasie of mucosa clearly far less pronounced compared to the acid.
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate, Wistar Han/BGA, 5 animals/sex.
(100) (102)

Species: rat **Sex:** male/female
Strain: other: Wistar Han/BGA
Route of admin.: oral feed
Exposure period: 90 days
Frequency of treatment: daily
Post. obs. period: 1 group for 0,1 or 4% respectively over 90 and 180 days
Doses: 0,2; 0,5; 1 and 4% (= 166, 415, 830, 3320mg/kg B.W.)
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Result: Wistar Han/BGA, 10 animals/sex.
Clinical and hematological examination and organ weights without abnormalities.
Forestomach males: hyperkeratosis and hyperplasia of mucosa, at 4% 1/10 atypical basal cell proliferation and 5/10 dysplasia. Forestomach females: hyperkeratosis and hyperplasia at 4% (hyperkeratosis also in controls) in differnt regions of forestomach. Effects largely reversible during 90-day post exposure observation period. After 180 days appearance of first agerelated changes in the forestomach.
NOEL: male: 0.2 %, female 1%
Source: BASF AG Ludwigshafen

(103)

Species: rat **Sex:** male
Strain:
Route of admin.: oral feed
Exposure period: 56 days
Frequency of treatment: daily
Post. obs. period:
Doses: 20000 and 40000ppm
Control Group: yes
Method:
Year: **GLP:**
Test substance: other TS
Result: 30% and 70% soy protein diets were used which were partly supplemented with vitamin B12. Reduction in body weight occurred in comparison to the soy protein diets without propionate addition. This was more pronounced in the 30% diet and independent of vit. B12 supplementation.
No other toxicological parameters were investigated.
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate

(104)

Species: rat **Sex:** male/female
Strain: Wistar
Route of admin.: oral feed
Exposure period: 7 days
Frequency of treatment: continued
Post. obs. period: no
Doses: 4 % in diet
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Result: The test- and control groups consisted of 5 male and 5 female rats. No significant clinical signs were recorded during the treatment.
The stomach walls of the treated rats were occasionally thickened and the mucosal surface was discoloured in several animals. In the forestomach of treated rats acanthosis, epithelial vacuolation and oedema of the lamina propria were reported. In the limiting ridge an increased number of mitotic figures were seen.
Source: BASF AG Ludwigshafen

(105) (106)

Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of admin.: oral feed
Exposure period: 90 days
Frequency of treatment: daily
Post. obs. period: 42 days, 10 rats per sex of control, 6200 and 50000ppm groups
Doses: 6200, 12500, 25000, 50000ppm (=517;1042;2083;4167mg/kg b.w.)
Control Group: yes, concurrent no treatment
NOAEL: 6200 ppm
Method: other: BASF-Test
Year: **GLP:** no
Test substance: other TS
Result: 20 rats per sex and dosage, 10 rats per sex and dosage for post- exposure-observation-period
50000ppm: feed intake and body weight gain of male animals reduced, no other clinical, hematological or clinicochemical effects, single slight deviations of absolute and relative organ weights without pathological significance, no macroscopic findings, proliferation-acanthosis and retention-hyperceratosis of forestomach mucosa. Reversibility in post-exposure-observation-period. 25000 and 12500ppm: dose-dependent occurance of forestomach- lesions as in the high dosage group, no significant other effects.
Source: BASF AG Ludwigshafen
Test substance: Propionsaeure technisch

(58) (107)

Species: rat **Sex:** male/female
Strain: Sprague–Dawley
Route of admin.: oral feed
Exposure period: 28 days
Frequency of treatment: daily
Post. obs. period:
Doses: 10000, 20000, 50000ppm
Control Group: yes, concurrent no treatment
Method: other: BASF–Test
Year: **GLP:** no
Test substance: other TS
Result: 10 rats per sex and dosage group. Substance intake approx. 800, 1500 and 3900 mg/kg b.w. (Calc. from feed consumption). 50000 ppm: decrease in weight gain of the male animals, no other clinical, hematological or clinicochemical effects, decrease in absolute liverweight of male animals, no change in relative organweights, histologically detected proliferation–acanthosis and retention–hyperceratosis of the forestomach mucosa. 20000 and 10000 ppm: dose–dependent occurence of mucosal lesions of forestomach, no other symptoms.
Source: BASF AG Ludwigshafen

(58) (108)

Species: rat **Sex:** male/female
Strain: other: albino, mongrels
Route of admin.: oral feed
Exposure period: 110 days
Frequency of treatment: daily
Post. obs. period:
Doses: about 5% (50000ppm = 3300mg/kg)
Control Group:
Method:
Year: **GLP:**
Test substance:
Result: 5 rats.
No systemic toxicity.
1/5 early death. 3/4 umbilicate or warty lesions of forestomach mucosa, 1/4 no abnormalities. Hyperkeratosis and hyperplasia of forestomach mucosa. No lesions in the glandular stomach. Similar effects after treatment with butyric acid (even more effective) and valeric acid.
Source: BASF AG Ludwigshafen

(58) (96)

Species: rat **Sex:** female
Strain: other: Wistar (SLC)
Route of admin.: oral feed
Exposure period: 1 year
Frequency of treatment: daily
Post. obs. period:
Doses: 2% (20000ppm = 1320mg/kg), calculated total intake 185g/animal
Control Group: yes, concurrent no treatment
NOAEL: 2 %
Method:
Year: **GLP:**
Test substance: other TS
Remark: Japanes article with tables and abstracts in english.
Result: Very slight retardation of growth rate (b.w. at the end of the study 290g versa 299g in control). No hematological, clinicochemical or urinalytic changes. No changes in organ weights. Histopathology: different spontaneous findings without substance relation, thereof 2 mammary tumours and 1 myxoma of the uterus. These findings are considered to be not substance related because in a test group fed simultaniously with 2% sodium propionate and 5% sorbic acid no such changes occured.
(40 animals per group)
Source: BASF AG Ludwigshafen
Test substance: sodium propionate

(58) (97)

Species: rat **Sex:** male/female
Strain: Wistar
Route of admin.: oral feed
Exposure period: 1 year
Frequency of treatment: daily
Post. obs. period:
Doses: The animals were maintained on a feed consisting in 75% bread which was baked under addition of the 50 fold amount of 4 bread additives and bleached flour. One of the additives was 5% sodium propionate.
Control Group: yes
Method:
Year: **GLP:**
Test substance: other TS
Result: The animals were maintained on a feed consisting in 75% bread which was baked under addition of the 50 fold amount of 4 bread additives and bleached flour. One of the additives was 5% sodium propionate.
Interim sacrifices were performed and a number of organs were examined histologically. No clinical nor pathological effects were observed. Therefore the authors conclude that neither the single substances nor their mixture cause toxic effects. The complex mixture of substances and conduct of the study make it difficult to judge on the real effect, if at all for single substances.
Source: BASF AG Ludwigshafen

Test substance: Sodium propionate, 27 animals per sex (58) (60) (98) (48)

Species: rat **Sex:** male
Strain: Wistar
Route of admin.: oral feed
Exposure period: 32 weeks
Frequency of treatment: daily
Post. obs. period:
Doses: The animals were maintained on a feed consisting in 75% of a bakiing mixture for bread which contained the 50 fold amount of 4 bread additives and bleached flour. One of the additives was 5% sodium propionate.
Control Group: yes
Method:
Year: **GLP:**
Test substance: other TS
Result: The animals were maintained on a feed consisting in 75% of a baking mixture for bread which contained the 50 fold amount of 4 bread additives and bleached flour. One of the additives was 5% sodium propionate.
Groups fed with diets containing 5% propionate show a reduction in body weight gain but no substance related histopathological effects were observed. The study was furthermore complicated by infections in different testgroups. The complex mixture of substances and conduct of the study make it difficult to judge on the real effect, if at all for single substances.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate, 30 animals (58) (99)

Species: rat **Sex:** male/female
Strain: Wistar
Route of admin.: oral feed
Exposure period: f 4 weeks, m 8 weeks
Frequency of treatment: daily
Post. obs. period: 1 group m 8 weeks
Doses: 4% (40000ppm = 3320mg/kg KGW)
Control Group: yes
Method:
Year: **GLP:**
Test substance: other TS
Result: Wistar Han/BGA, 5 animals/sex
Clinical examination and organ weights without abnormalities. Forestomach 4 week exposure: hyperkeratosis and hyperplasie of l limiting ridge, isolated ulcerations in 4/5 animals. Forestomach 8 week exposure: more pronounced lesions in number and expression.
Reversibility of changes in 8 week post exposure observation period.
Similar effects produced by 4 and 6% acetic acid or 4% capronic acid.

Source: BASF AG Ludwigshafen
(58) (109)

Species: rat **Sex:** male
Strain: Wistar
Route of admin.: oral feed
Exposure period: 4 weeks
Frequency of treatment: daily
Post. obs. period:
Doses: 4% (40000ppm = 3320mg/kg KGW)
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Result: Clinical examination and organ weights without abnormalities. Forestomach : limiting ridge slightly thickend in 3/5, mucosa macroscopically unchanged. Histology: hyperkeratosis of mucosa, hyperplasia of basal cells at the limiting ridge in 1/5. In general obviously slighter forestomach-changes as compared to the acid. Similar effects produced by 4% Sodium acetate.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate, Wistar Han/BGA, 5 animals
(58) (109)

Species: rat **Sex:** male/female
Strain: Wistar
Route of admin.: oral feed
Exposure period: f 4 weeks, m 8 weeks
Frequency of treatment: daily
Post. obs. period:
Doses: 4% (40000ppm = 3320mg/kg KGW)
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Result: Reduction of feed consumption, body weight gain and abs. organ weights.
Forestomach: 4 week exposure: Slight thickening of limiting ridge. Hyperkeratosis and hyperplasie of mucosa clearly far less pronounced compared to the acid.
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate, Wistar Han/BGA, 5 animals/sex.
(58) (109)

Species: rat **Sex:** male/female
Strain: other: Wistar Han/BGA
Route of admin.: oral feed
Exposure period: 90 days
Frequency of treatment: daily
Post. obs. period: 1 group for 0,1 or 4% respectively over 90 and 180 days
Doses: 0,2; 0,5; 1 and 4% (= 166, 415, 830, 3320mg/kg B.W.)
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Result: Wistar Han/BGA, 10 animals/sex.
Clinical and hematological examination and organ weights without abnormalities.
Forestomach males: hyperkeratosis and hyperplasia of mucosa, at 4% 1/10 atypical basal cell proliferation and 5/10 dysplasia. Forestomach females: hyperkeratosis and hyperplasia at 4% (hyperkeratosis also in controls) in differnt regions of forestomach. Effects largely reversible during 90–day post exposure observation period. After 180 days appearance of first agerelated changes in the forestomach.
NOEL: male: 0.2 %, female 1%
Source: BASF AG Ludwigshafen

(109)

Species: rat **Sex:** male/female
Strain: Wistar
Route of admin.: oral feed
Exposure period: 7 days
Frequency of treatment: continued
Post. obs. period: no
Doses: 4 % in diet
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Result: The test– and control groups consisted of 5 male and 5 female rats. No significant clinical signs were recorded during the treatment.
The stomach walls of the treated rats were occasionally thickened and the mucosal surface was discoloured in several animals. In the forestomach of treated rats acanthosis, epithelial vacuolation and oedema of the lamina propria were reported. In the limiting ridge an increased number of mitotic figures were seen.
Source: BASF AG Ludwigshafen

(106) (110)

Species: rat **Sex:** male
Strain: Wistar
Route of admin.: gavage
Exposure period: 1; 3; 7; 14 or 28 days
Frequency of treatment: daily
Post. obs. period: no
Doses: 300 mg/kg
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Result: No treatment related findings in the forestomach were found after 1 and 3 days of treatment.
After 7 and more days of treatment thickening of the forestomach mucosa respectively hyperplasia of the squamous epithelium with marked desquamation were found.
Source: BASF AG Ludwigshafen

(111)

Species: mouse **Sex:** male/female
Strain: B6C3F1
Route of admin.: oral feed
Exposure period: 7 days
Frequency of treatment: continued
Post. obs. period: no
Doses: 4 % in diet
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Result: Test and control groups consisted of 5 male and 5 female mice. No significant clinical signs were recorded during the treatment. One male and two female mice receiving propionic acid in diet had thick stomach walls. In forestomach basal cell hyperplasia and epithelial downgrowths were reported, no treatment–related findings were detected in the limiting ridge.
Source: BASF AG Ludwigshafen

(112) (106)

Species: mouse **Sex:** male/female
Strain: B6C3F1
Route of admin.: oral feed
Exposure period: 7 days
Frequency of treatment: continued
Post. obs. period: no
Doses: 4 % in diet
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Result: Test and control groups consisted of 5 male and 5 female mice. No significant clinical signs were recorded during the treatment. One male and two female mice receiving propionic acid in diet had thick stomach walls. In forestomach basal cell hyperplasia and epithelial downgrowths were reported, no treatment-related findings were detected in the limiting ridge.
Source: BASF AG Ludwigshafen

(106) (110)

Species: mouse **Sex:** female
Strain: other: Crl:CD1(ICR)BR
Route of admin.: dermal
Exposure period: 90 days
Frequency of treatment: each working day
Post. obs. period: no
Doses: 50ul of 8%, 10% and 14% aqueous solution (133, 167, 233 mg/kg bw)
Control Group: yes
NOAEL: < 8 %
Method: OECD Guide-line 409 "Subchronic Oral Toxicity - Non-rodent: 90-day Study"
Year: 1981 **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Remark: At the beginning of the study the applied concentrations were 6%, 8% and 10%. When after 3 weeks of treatment no dermal effects occured the low concentration was increased to 14%.
Result: No influence of treatment on body weight and body weight gain. Further clinical effects of systemic toxicity were not described and no clinico-chemical investigation or pathology other than for skin lesions was performed.
Skin effects:
14%: all animals showed skin lesions ranging from erythema and crust formation to ulceration. This was affirmed pathologically and histology revealed acanthosis and fibrous condensation with inflammation of connective tissue.
10%: 6/10 animals showed skin lesions which were in general less pronounced than in the high concentration. The same histological findings as in the high concentration group occured. 8%: no clinically detectable skin lesions were seen but in 5 animals histological alterations as described above

could be detected.
The results of the study indicate that a non–irritant concentration lies below 8% and the MTD between 10 and 14%.

Source: BASF AG Ludwigshafen

(113)

Species: Syrian hamster **Sex:** male/female
Strain:
Route of admin.: oral feed
Exposure period: 7 days
Frequency of treatment: continued
Post. obs. period: no
Doses: 4 % in diet
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Result: Test– and control group consisted of 5 male and 5 female rats. No significant clinical signs were recorded during the treatment.
The stomachs of the hamsters recieving propionic acid in diet were normal but one hamster had haemorrhagic lungs. In the forestomachs nuclear vacuolation and thinning of the epithelium in the limiting ridges was reported.
Source: BASF AG Ludwigshafen

(112) (106)

Species: Syrian hamster **Sex:** male/female
Strain:
Route of admin.: oral feed
Exposure period: 7 days
Frequency of treatment: continued
Post. obs. period: no
Doses: 4 % in diet
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Result: Test– and control group consisted of 5 male and 5 female rats. No significant clinical signs were recorded during the treatment.
The stomachs of the hamsters recieving propionic acid in diet were normal but one hamster had haemorrhagic lungs. In the forestomachs nuclear vacuolation and thinning of the epithelium in the limiting ridges was reported.
Source: BASF AG Ludwigshafen

(106) (110)

Species: dog **Sex:** male/female
Strain: Beagle
Route of admin.: oral feed
Exposure period: 90 days
Frequency of treatment: daily
Post. obs. period: control and high dosage for 6 weeks
Doses: 3000, 10000, 30000 ppm
Control Group: yes, concurrent no treatment
Method: OECD Guide-line 409 "Subchronic Oral Toxicity - Non-rodent: 90-day Study"
Year: 1981 **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Result: 4 animals per sex and exposure and untreated postexposure group. Substance intake about 200, 700 and 2000 mg/kg b.w. High dosage: lack of appetite, no other substance related clinical, hematological, clinico-chemical effect. More pronounced expression of spontaneous epithelial hyperplasia of esophageal mucosa as compared to control. This finding was reversible in the post exposure observation period. No other pathological findings. Mid- and low-dosage groups without substance-related findings.
Source: BASF AG Ludwigshafen

(103) (114)

Species: dog **Sex:** male
Strain: Beagle
Route of admin.: oral feed
Exposure period: 90 days
Frequency of treatment: daily
Post. obs. period:
Doses: 14500,43500ppm
Control Group: yes, concurrent no treatment
Method:
Year: **GLP:** yes
Test substance: other TS
Remark: No hematological or clinicochemical parameters determined.
Result: High dose: diarrhoea and vomiting in all animals, low dosage: only in one dog. Similar spontaneous epithelial hyperplasia of esophageal mucosa in all groups including control without relation to treatment.
Source: BASF AG Ludwigshafen
Test substance: Calcium propionat

(115) (116)

Species: dog **Sex:** male/female
Strain: Beagle
Route of admin.: oral feed
Exposure period: 90 days
Frequency of treatment: daily
Post. obs. period: control and high dosage for 6 weeks
Doses: 3000, 10000, 30000 ppm
Control Group: yes, concurrent no treatment
Method: OECD Guide-line 409 "Subchronic Oral Toxicity - Non-rodent: 90-day Study"
Year: 1981 **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Result: 4 animals per sex and exposure and untreated postexposure group. Substance intake about 200, 700 and 2000 mg/kg b.w. High dosage: lack of appetite, no other substance related clinical, hematological, clinico-chemical effect. More pronounced expression of spontaneous epithelial hyperplasia of esophageal mucosa as compared to control. This finding was reversible in the post exposure observation period. No other pathological findings. Mid- and low-dosage groups without substance-related findings.
Source: BASF AG Ludwigshafen

(109) (114) (117)

Species: dog **Sex:** male
Strain: Beagle
Route of admin.: oral feed
Exposure period: 90 days
Frequency of treatment: daily
Post. obs. period:
Doses: 14500,43500ppm
Control Group: yes, concurrent no treatment
Method:
Year: **GLP:** yes
Test substance: other TS
Remark: No hematological or clinicochemical parameters determined.
Result: High dose: diarrhoea and vomiting in all animals, low dosage: only in one dog. Similar spontaneous epithelial hyperplasia of esophageal mucosa in all groups including control without relation to treatment.
Source: BASF AG Ludwigshafen
Test substance: Calcium propionat

(109) (118)

Species: hen **Sex:** male
Strain:
Route of admin.: oral feed
Exposure period: 38 days
Frequency of treatment: daily
Post. obs. period:
Doses: 3%
Control Group:
Method: other: BASF–Test
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Remark: The study intended to investigate the influence of propionic acid in feed on Salmonella infection. In 1 group PA was the sole aditive, in several other groups additionally Monensin and Avotan were given.
Result: No histopathological findings in crop, esophagus stomach and bowel.
Source: BASF AG Ludwigshafen

(47) (119)

Species: hen **Sex:** male
Strain:
Route of admin.: oral feed
Exposure period: 38 days
Frequency of treatment: daily
Post. obs. period:
Doses: 3%
Control Group:
Method: other: BASF–Test
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Remark: The study intended to investigate the influence of propionic acid in feed on Salmonella infection. In 1 group PA was the sole aditive, in several other groups additionally Monensin and Avotan were given.
Result: No histopathological findings in crop, esophagus stomach and bowel.
Source: BASF AG Ludwigshafen

(58) (120)

Species: monkey **Sex:** no data
Strain:
Route of admin.: oral feed
Exposure period: 9 weeks
Frequency of treatment: continued
Post. obs. period: keine Angaben
Doses: 2 % Natriumpropionat in diet (= 420 mg/kg bw/day)
Control Group: no data specified
Method:
Year: **GLP:**
Test substance: other TS
Result: There were no overt toxic effects recorded in 12 monkeys that had recieved a diet containing 2 % sodium propionate for 9 weeks. Examination was limited to blood and liver.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(121)

Species: pig **Sex:**
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses: 3 and 4%
Control Group:
Method:
Year: **GLP:**
Test substance:
Remark: No full document available, excerpt of pathology report.
Result: 3 or 4% propionic acid in pig–feed resulted in gastritis fibrinosa and Entritis catarrhalis desquamativa of small intestine. Also fat accumulation in single liver cells or small cell clusters occured.
Source: BASF AG Ludwigshafen

(122)

Species: pig **Sex:**
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses: 1,2 and 3%
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: No full document available, excerpt from part of the report.
Result: 12 animals per group. Fattening from 24 to 93kg.
No negative influence on fattening, feed utilisation and meat quality.
Source: BASF AG Ludwigshafen

(123)

Species: pig **Sex:**
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses: 1,2 and 3%
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: No full document available, excerpt from part of the report.
Result: 12 animals per group. Fattening from 24 to 93kg.
No negative influence on fattening, feed utilisation and meat quality.
Source: BASF AG Ludwigshafen

(122)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: S.typhimurium NTP standardbattery
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen

(124)

Type: Ames test
System of testing: S.typhimurium TA98,100
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium–propionate

(125)

Type: Ames test
System of testing: S.typhimurium TA 92,94,98,100,1535,1537
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Remark: –5mg/plate
Table not readable, but result "negative" is assumed.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(100) (126) (127)

Type: Ames test
System of testing: S.typhimurium TA 92,94,98,100,1535,1537
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Remark: –10mg/plate.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(100) (126)

Type: Ames test
System of testing: S.typhimurium TA 98,100,1535,1537,1538
Concentration: 0,095% (0,95 mg/ml)
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: S9 from rat, mouse and hamster.
Plate- and suspensiontest
Source: BASF AG Ludwigshafen
(100) (48) (128)

Type: Ames test
System of testing: S.typhimurium TA98,100,1353,1357
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: 0,01-10ul/plate.
Source: BASF AG Ludwigshafen
(100) (129)

Type: Ames test
System of testing: S.typhimurium TA 98, 100, 1535, 1537, 1538
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate
(130)

Type: Ames test
System of testing: S.typhimurium TA98,100
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium-propionate
(131)

Type: Ames test
System of testing: S.typhimurium TA 92,94,98,100,1535,1537
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Remark: -5mg/plate
Table not readable, but result "negative" is assumed.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(58) (126) (127)

Type: Ames test
System of testing: S.typhimurium TA 92,94,98,100,1535,1537
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Remark: -10mg/plate.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(58) (126)

Type: Ames test
System of testing: S.typhimurium TA 98,100,1535,1537,1538
Concentration: 0,095% (0,95 mg/ml)
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: S9 from rat, mouse and hamster.
Plate- and suspensiontest
Source: BASF AG Ludwigshafen

(58) (48) (128)

Type: Ames test
System of testing: S.typhimurium TA98,100,1353,1357
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: 0,01-10ul/plate.
Source: BASF AG Ludwigshafen
(58) (132)

Type: Cytogenetic assay
System of testing: CHL cells
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(125) (133)

Type: Cytogenetic assay
System of testing: CHL-cells
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Remark: -2mg/ml.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(100) (126) (127)

Type: Cytogenetic assay
System of testing: CHL-cells
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Remark: -2mg/ml.
slight increase of aberrations in highest concentration, no effect at 1mg/ml.
Source: BASF AG Ludwigshafen

Test substance: Calcium propionate (100) (126)

Type: Cytogenetic assay
System of testing: Human WI38 cells
Concentration: 0,4; 4; 40 mg/l
Metabolic activation:
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Calciumpropionate (134)

Type: Cytogenetic assay
System of testing: CHL cells
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate (131) (133)

Type: Cytogenetic assay
System of testing: CHL–cells
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Remark: –2mg/ml.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate (58) (126) (127)

Type: Cytogenetic assay
System of testing: CHL–cells
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Remark: –2mg/ml.
slight increase of aberrations in highest concentration, no effect at 1mg/ml.
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate

(58) (126)

Type: Cytogenetic assay
System of testing: Human WI38 cells
Concentration: 0,4; 4; 40 mg/l
Metabolic activation:
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Calciumpropionate

(135)

Type: DNA damage and repair assay
System of testing: Bac.subtilis
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(125)

Type: DNA damage and repair assay
System of testing: E.coli WP2, WP67(uvrA-,polA-) und CM871(uvrA-,recA-,lexA-)
Concentration:
Metabolic activation: without
Result:
Method:
Year: **GLP:**
Test substance:
Remark: Dose: 1, 5 and 25ul.
Inhibition of strains WP67 and CM871 stronger than WP2.
Result is not evaluated by the author.
Source: BASF AG Ludwigshafen
(100) (129)

Type: DNA damage and repair assay
System of testing: Bac.subtilis
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(131)

Type: DNA damage and repair assay
System of testing: E.coli WP2, WP67(uvrA-,polA-) und CM871(uvrA-,recA-,lexA-)
Concentration:
Metabolic activation: without
Result:
Method:
Year: **GLP:**
Test substance:
Remark: Dose: 1, 5 and 25ul.
Inhibition of strains WP67 and CM871 stronger than WP2.
Result is not evaluated by the author.
Source: BASF AG Ludwigshafen
(58) (132)

Type: Sister chromatid exchange assay
System of testing: V79 cells
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: 0,1-33mM.
Source: BASF AG Ludwigshafen
(100) (129)

Type: Sister chromatid exchange assay
System of testing: V79 cells
Concentration:
Metabolic activation: no data
Result:
Method:
Year: **GLP:**
Test substance:
Remark: Slightly elevated SCE. Negative control in comparison to Sodium butyrate. No further information.
Source: BASF AG Ludwigshafen
(136)

Type: Sister chromatid exchange assay
System of testing: human lymphocytes
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: slightly increase in SCE at 2.5 mM is described. According to the authors this weak SCE induction may be related to altered culture conditions. Some carboxylic acids were studied and the maximum response was, at most, 1.8 times (crotonic acid). For propionic acid the response was about 1.2 times. In contrast to the authors the result should be judged as negative.
Source: BASF AG Ludwigshafen
(137)

Type: Sister chromatid exchange assay
System of testing: V79 cells
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: 0,1-33mM.
Source: BASF AG Ludwigshafen
(58) (132)

Type: other: DNA repair recassay
System of testing: Bac.subtilis H17(rec+), M45(rec-)
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Remark: paper disk method
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate
(130)

Type: other: E.coli reverse mutation assay
System of testing: E.coli WP2 hcr trp
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate
(130)

Type: other: Gene conversion assay
System of testing: Sac. cerevisiae D4
Concentration: 2,5% 25 mg/ml
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen
(100) (48) (128)

Type: other: Gene conversion assay
System of testing: Sac. cerevisiae D4
Concentration: 2,5% 25 mg/ml
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Source: BASF AG Ludwigshafen
(58) (48) (128)

Type: other: Micronucleus Test
System of testing: Tradescantia paludosa clone 03
Concentration: 0,25-1%
Metabolic activation: without
Result: ambiguous
Method:
Year: **GLP:**
Test substance:
Remark: Increase of the number of micronuclei in highest concentration.
Source: BASF AG Ludwigshafen
(138)

Type: other: Micronucleus Test
System of testing: Tradescantia paludosa clone 03
Concentration: 0,2-1 mM
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate
(138)

Type: other: Punktmutation
System of testing: silkworm
Concentration:
Metabolic activation:
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(125)

Type: other: Punktmutation
System of testing: silkworm
Concentration:
Metabolic activation:
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(131)

Type: other: SOS-Chromotest
System of testing: E.coli PQ37
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: 0,01-10mM.
Source: BASF AG Ludwigshafen

(100) (129)

Type: other: SOS-Chromotest
System of testing: E.coli PQ37
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: 0,01-10mM.
Source: BASF AG Ludwigshafen

(58) (132)

Type: other
System of testing: E.coli PQ37
Concentration: 0,3-33,3 mM
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: Toxicity at 10 and 33,3mM.
Source: BASF AG Ludwigshafen

(139)

Type: other
System of testing: E.coli Sd4-73
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: Reversion from streptomycin dependence to independence. Paper disk method.
Source: BASF AG Ludwigshafen

(140)

Type: other
System of testing: E. coli PQ37
Concentration:
Metabolic activation:
Result:
Method:
Year: **GLP:**
Test substance: other TS
Remark: Induction of SOS function by UV irradiation was not inhibited by calcium propionate up to 500ug/l.
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate

(141)

Type: other
System of testing: Bac.subtilis H17(rec+),M45(rec-)
Concentration:
Metabolic activation: without
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Remark: 50ul of 1% solution on paper disk
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate

(142)

Type: other
System of testing: S.typhimurium G46 and TA1530, Sacch.cerevisiae D3
Concentration:
Metabolic activation:
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate

(134)

Type: other
System of testing: S.typhimurium G46 and TA1530, Sacch.cerevisiae D3
Concentration:
Metabolic activation:
Result: negative
Method:
Year: **GLP:**
Test substance: other TS
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate

(135)

5.6 Genetic Toxicity 'in Vivo'

Type: Cytogenetic assay
Species: rat **Sex:**
Strain:
Route of admin.:
Exposure period:
Doses:
Result:
Method:
Year: **GLP:**
Test substance: other TS
Remark: bone marrow, no further details
Result: negativ
Sodium–propionate, bone marrow, no further details
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(143)

Type: Cytogenetic assay
Species: rat **Sex:**
Strain:
Route of admin.: oral unspecified
Exposure period: Single dose and five doses
Doses: 50, 500, 5000mg/kg
Result:
Method:
Year: **GLP:**
Test substance: other TS
Result: No increase of chromosome aberrations in bone marrow cells
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate

(135)

Type: Cytogenetic assay
Species: rat **Sex:**
Strain:
Route of admin.:
Exposure period:
Doses:
Result:
Method:
Year: **GLP:**
Test substance: other TS
Remark: bone marrow, no further details
Result: negativ
Sodium–propionate, bone marrow, no further details
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(131)

Type: Dominant lethal assay
Species: rat **Sex:**
Strain:
Route of admin.: oral unspecified
Exposure period: Single dose
Doses: 50, 500, 5000mg/kg
Result:
Method:
Year: **GLP:**
Test substance: other TS
Result: No dominant lethal mutations detected
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate

(135)

Type: Micronucleus assay
Species: Chinese hamster **Sex:** male/female
Strain:
Route of admin.: i.p.
Exposure period: once
Doses: 5ml 2,5% propionic acid/kg b.w. (=125mg/kg)
Result:
Method:
Year: **GLP:**
Test substance:
Result: Chinese hamster. 6 animals/sex. Sacrifice intervals 12, 24 and 48h p.inj.. Toxicity: 4/36 died.
No increase in number of micronuclei.
Source: BASF AG Ludwigshafen
(100) (129)

Type: Micronucleus assay
Species: Chinese hamster **Sex:** male/female
Strain:
Route of admin.: i.p.
Exposure period: once
Doses: 5ml 2,5% propionic acid/kg b.w. (=125mg/kg)
Result:
Method:
Year: **GLP:**
Test substance:
Result: Chinese hamster. 6 animals/sex. Sacrifice intervals 12, 24 and 48h p.inj.. Toxicity: 4/36 died.
No increase in number of micronuclei.
Source: BASF AG Ludwigshafen
(58) (132)

Type: other: Host mediated assay
Species: mouse **Sex:**
Strain:
Route of admin.: oral unspecified
Exposure period: Single dose and five doses
Doses: 50, 500, 5000mg/kg
Result:
Method:
Year: **GLP:**
Test substance: other TS
Result: Increase in reversion frequency of S.typhimurium G-46 but not dose related. No mutations in strain TA1530 and Saccharomyces cerevisiae D3.
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate
(135)

5.7 Carcinogenicity

Species: rat **Sex:** male
Strain: other: Wistar (Han-BGA)
Route of admin.: oral feed
Exposure period: 10 animals/group 25 weeks; 20 animals/group until end of life
Frequency of treatment: daily
Post. obs. period: no
Doses: 0,4; 4% (4000; 40000ppm = 264; 2640mg/kg b.w.)
Result:
Control Group: yes
Method: other
Year: **GLP:** no
Test substance: other TS
Result: 25 weeks and 4%: hyperkeratotic and -plastic changes of forestomach mucosa, especially at the limiting ridge, 6/10 epidermal hyperplasia with beginning ulceration or papilloma formation, erosive lesions in the glandular stomach.
25 weeks and 0,4%: hyperkeratosis, hyperplasia of limiting ridge. Lifetime groups:
Survival: Control 125+/-30 weeks, 0,4% 122+/-29 weeks, 4% 121+/- 31 weeks.
Effects 4%: 17/20 papillomas partly with horny pearls or cysts, described as precancerous lesions in 5 animals. Strong mucosal hyperplasia of forestomach. 19/20 dysplasia of glanular stomach mucosa (13 multiple), 1/20 Cyst in the pyloroduodenal region, 1/20 adenomalike dysplasial proliferation in pyloric region, 1/20 fibroma and leiomyoma of jejunum. Effects 0,4%: hyperkeratosis and slight hyperplasia of limiting ridge, 10/20 proliferation of basal cells, 13/20 dysplasia of glandular stomach, 1/20 adenocarcinoma of pyloric region, 1/20 cyst in region of Brunners gland and adenomalike dysplasial proliferation in pyloric region. Control: 5/20 dysplasia of glandular stomach.
Source: BASF AG Ludwigshafen
Test substance: Propionsaeure und ihre Salze

(144) (100) (145)

Species: rat **Sex:** male
Strain: other: Wistar (Han-BGA)
Route of admin.: oral feed
Exposure period: 10 animals/group 25 weeks; 20 animals/group until end of life
Frequency of treatment: daily
Post. obs. period: no
Doses: 0,4; 4% (4000; 40000ppm = 264; 2640mg/kg b.w.)
Result:
Control Group: yes
Method: other
Year: **GLP:** no
Test substance: other TS
Result: 25 weeks and 4%: hyperkeratotic and -plastic changes of forestomach mucosa, especially at the limiting ridge, 6/10 epidermal hyperplasia with beginning ulceration or papilloma formation, erosive lesions in the glandular stomach.
25 weeks and 0,4%: hyperkeratosis, hyperplasia of limiting ridge. Lifetime groups:
Survival: Control 125+/-30 weeks, 0,4% 122+/-29 weeks, 4% 121+/- 31 weeks.
Effects 4%: 17/20 papillomas partly with horny pearls or cysts, described as precancerous lesions in 5 animals. Strong mucosal hyperplasia of forestomach. 19/20 dysplasia of glanular stomach mucosa (13 multiple), 1/20 Cyst in the pyloroduodenal region, 1/20 adenomalike dysplasial proliferation in pyloric region, 1/20 fibroma and leiomyoma of jejunum. Effects 0,4%: hyperkeratosis and slight hyperplasia of limiting ridge, 10/20 proliferation of basal cells, 13/20 dysplasia of glandular stomach, 1/20 adenocarcinoma of pyloric region, 1/20 cyst in region of Brunners gland and adenomalike dysplasial proliferation in pyloric region. Control: 5/20 dysplasia of glandular stomach.
Source: BASF AG Ludwigshafen
Test substance: Propionsaeure und ihre Salze

(58) (109) (145)

Species: rat **Sex:** male
Strain: Fischer 344
Route of admin.: other: keine Angabe
Exposure period: 6 Wochen
Frequency of treatment:
Post. obs. period:
Doses: keine Angabe
Result:
Control Group:
Method:
Year: **GLP:**
Test substance: other TS
Remark: The original article from Ito et al.: Carcinogenesis 9, 387-394 (1988) contains no data on sodium propionate.
Result: In this review article on a standardized protocol for a medium term bioassay model for carcinogenesis with DEN

initiation and partial hepatectomy sodium propionate occures in a list of chemicals with positive results.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(146)

5.8 Toxicity to Reproduction

-

5.9 Developmental Toxicity/Teratogenicity

Species: rat **Sex:**
Strain: Wistar
Route of admin.: oral unspecified
Exposure period: 10 days, days 6-15
Frequency of treatment: daily
Duration of test:
Doses: 3, 14, 65, 300mg/kg
Control Group: other: sham treated
Method:
Year: **GLP:**
Test substance: other TS
Result: No maternal or fetal abnormalities detected.
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate

(147)

Species: mouse **Sex:**
Strain: CD-1
Route of admin.: oral unspecified
Exposure period: 10 days, days 6-15
Frequency of treatment: daily
Duration of test:
Doses: 3, 14, 65, 300mg/kg
Control Group: other: sham treated
Method:
Year: **GLP:**
Test substance: other TS
Result: No maternal or fetal abnormalities detected.
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate

(147)

Species: rabbit **Sex:**
Strain: other: Hollaender
Route of admin.: oral unspecified
Exposure period: 13 days, days 6-18
Frequency of treatment: daily
Duration of test:
Doses: 4, 19, 86, 400mg/kg
Control Group: other: sham treated
Method:
Year: **GLP:**
Test substance: other TS
Result: No maternal or fetal abnormalities detected.
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate

(147)

Species: hamster **Sex:**
Strain:
Route of admin.: oral unspecified
Exposure period: 5 days, days 6-10
Frequency of treatment: daily
Duration of test:
Doses: 4, 19, 86, 400mg/kg
Control Group: other: sham treated
Method:
Year: **GLP:**
Test substance: other TS
Result: No maternal or fetal abnormalities detected.
Source: BASF AG Ludwigshafen
Test substance: Calcium propionate

(147)

Species: **Sex:**
Strain:
Route of admin.: other: Injection
Exposure period:
Frequency of treatment:
Duration of test:
Doses: 10 mg/egg
Control Group:
Method:
Year: **GLP:**
Test substance: other TS
Result: Injection of up to 10mg/egg into air cell or yolc sac of preincubation or 96h incubated hen eggs resulted in LD50 values between 3,2 and 6,7mg/egg. There was a dose dependent increase in abnormalities after injection into the air cell but not after treatment via the yolc sac.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate

(148)

5.10 Other Relevant Information

Type: Cytotoxicity
Remark: erythroleucemic cells
Propionic acid induces erythroid differentiation of the cells at 1-2mM concentrations. Butyric acid is much more effective.
Source: BASF AG Ludwigshafen
(149)

Type: Cytotoxicity
Remark: colonic epithelial cells
Primary cultures of human epithelial cells from colon biopsies from patients with high risk of colon cancer were treated with psyllium fiber or short chain fatty acids. Propionic acid from 2-10mM decreased the number of viable cells to 45% and from 10-15mM increased the H3-Thymidine labeling index of the surviving cells to 120-140% of the control value.
Source: BASF AG Ludwigshafen
(150)

Type: Cytotoxicity
Remark: Lymphcytes
Mitogen induced proliferation of cultured lymphocytes is reversibly inhibited by propionic acid (1-10mM) without cytotoxicity (survival measured by trypan blue). Butyric acid is the most potent substance out of several short chain fatty acids.
Source: BASF AG Ludwigshafen
(151)

Type: Cytotoxicity
Remark: Yeast
Minimum inhibitory concentration in different yeast species (adapted to benzoic acid) at pH 3,5 was 2,5-13,5g/l. The inhibitory effect was not due to the pH.
Source: BASF AG Ludwigshafen
(152)

Type: Cytotoxicity
Remark: hum.leukemic lymphoblasts
CCRF-CEM cells.
After incubation in 5mM concentration the following ranking of cytotoxicity was established for short chain fatty acids by cell counting, H3-Thymidine incorporation and C14-release:
n-butyrate>propionate=n-valerate>i-butyrate>>acetate.
Source: BASF AG Ludwigshafen
(153)

Type: Cytotoxicity
Remark: HepG2 cells
PI50 = concentration which produces 50% reduction of protein content = 45mM
Source: BASF AG Ludwigshafen
(154)

Type: Cytotoxicity
Remark: colonic epithelial cells
Primary cultures of human epithelial cells from colon biopsies from patients with high risk of colon cancer were treated with psyllium fiber or short chain fatty acids. Propionic acid from 2–10mM decreased the number of viable cells to 45% and from 10–15mM increased the H3–Thymidine labeling index of the surviving cells to 120–140% of the control value.
Source: BASF AG Ludwigshafen
(150)

Type: Cytotoxicity
Remark: Lymphcytes
Mitogen induced proliferation of cultured lymphocytes is reversibly inhibited by propionic acid (1–10mM) without cytotoxicity (survival measured by trypan blue). Butyric acid is the most potent substance out of several short chain fatty acids.
Source: BASF AG Ludwigshafen
(151)

Type: Cytotoxicity
Remark: Yeast
Minimum inhibitory concentration in different yeast species (adapted to benzoic acid) at pH 3,5 was 2,5–13,5g/l. The inhibitory effect was not due to the pH.
Source: BASF AG Ludwigshafen
(152)

Type: Cytotoxicity
Remark: hum.leukemic lymphoblasts
CCRF–CEM cells.
After incubation in 5mM concentration the following ranking of cytotoxicity was established for short chain fatty acids by cell counting, H3–Thymidine incorporation and C14–release:
n–butyrate>propionate=n–valerate>i–butyrate>>acetate.
Source: BASF AG Ludwigshafen
(155)

Type: Cytotoxicity
Remark: HepG2 cells
PI50 = concentration which produces 50% reduction of protein content = 45mM
Source: BASF AG Ludwigshafen
(156)

Type: Metabolism
Remark: Summary of literature upto 1958.
Propionic acid is metabolized in mammals rapidly and entirely, the main pathway being from propionyl-CoA via Methylmalonyl-CoA after incorporation of CO2 to succinate, which is member of citric acid cycle. Minor pathways may be condensation of acetyl- and propionyl-CoA to form beta-Ketovalerianyl-CoA or metabolism to beta-alanine.
Source: BASF AG Ludwigshafen
(77)

Type: Metabolism
Remark: Summary of literature upto 1958.
Propionic acid is a natural intermediate in metabolism of odd- numbered fatty acids and amino acids (valine, isoleucine, threonine). 0-5% of volatile fatty acids in blood (0,18- 1,6mmol/l) are propionic acid. From in vitro studies metabolic rates up to 4,5g propionic acid/h for the liver of a 70kg man could be estimated.
Source: BASF AG Ludwigshafen
(77)

Type: Metabolism
Remark: Liver cell culture
Liver cell cultures of B12 deficient rats excert a decrease of propionate metabolism (1mM) to glucose or CO2. Addition of carnitin (10mM) increases the production of propionylcarnitin (10- ad fold) without altering the above pathway. Intraperitoneal administration of carnitin increases the urinary excretion of propionylcarnitin in Vit.B12 deficient rats.
Source: BASF AG Ludwigshafen
(157)

Type: Metabolism
Remark: rabbit
Oral administration (gavage) of 1000 or 3000mg/kg did not reduce acetonuria in alloxan diabetic rabbits but was lethal to 3/9 in the high dose. This was not the case in normal animals. 10mMol/kg (970mg/kg) produced no elevation in excretion of total short chain fatty acids but a shift towards excretion of acetic acid. In diabetic animals this treatment produced an increase in urinary excretion of ketone bodies, short chain fatty acid (acetic and butyric) and glucose. Propionic acid was not excreted.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(158)

Type: Metabolism
Remark: Summary of literature upto 1958.
Propionic acid is metabolized in mammals rapidly and entirely, the main pathway being from propionyl-CoA via Methylmalonyl-CoA after incorporation of CO2 to succinate, which is member of citric acid cycle. Minor pathways may be condensation of acetyl- and propionyl-CoA to form beta-Ketovalerianyl-CoA or metabolism to beta-alanine.

Source: BASF AG Ludwigshafen
(78)

Type: Metabolism
Remark: Summary of literature upto 1958.
Propionic acid is a natural intermediate in metabolism of odd- numbered fatty acids and amino acids (valine, isoleucine, threonine). 0-5% of volatile fatty acids in blood (0,18- 1,6mmol/l) are propionic acid. From in vitro studies metabolic rates up to 4,5g propionic acid/h for the liver of a 70kg man could be estimated.
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Type: Metabolism
Remark: Liver cell culture
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Source: BASF AG Ludwigshafen
(159)

Type: Metabolism
Remark: rabbit
Oral administration (gavage) of 1000 or 3000mg/kg did not reduce acetonuria in alloxan diabetic rabbits but was lethal to 3/9 in the high dose. This was not the case in normal animals. 10mMol/kg (970mg/kg) produced no elevation in excretion of total short chain fatty acids but a shift towards excretion of acetic acid. In diabetic animals this treatment produced an increase in urinary excretion of ketone bodies, short chain fatty acid (acetic and butyric) and glucose. Propionic acid was not excreted.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(158)

Type: Neurotoxicity
Remark: Ratte
1 ul injection of 120mM propionic acid solution into the dorsal hippocampus of anesthetized adult Spraque-Dawley rats (total amount = 8,88ug) did not induce histologically detectable neurotoxic brain lesions.
Source: BASF AG Ludwigshafen
(160)

Type: Toxicokinetics
Remark: rat
Vitamin B12 deficiency produced by soy bean diets led to an increase in urinary excretion of radioactivity from intraperitoneally injected H3-propionic acid. Parenteral supplementation of vit.B12 (3 doses of 5ug in 4weeks) turned excretion to normal.

Source: BASF AG Ludwigshafen
(104)

Type: other: Carrier–mediated transport of monocarboxylic acids in primary cultured epithelial cells from rabbit oral mucosa
Source: BASF AG Ludwigshafen
(161)

Type: other: Developmental toxicity of carboxylic acids to Xenopus embryos: A quantitative structure–activity relationship and computer–automated structure evaluation
Source: BASF AG Ludwigshafen
(162)

Type: other: Human data
Remark: case study

Daily doses of 6g in an adult showed no toxic effect. A sligt alkalinisation of urine occured.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(77) (88)

Type: other: Human data
Remark: clinical exp./ sensitization

chronic topical use of 10% sodium propionate solution in clinical trials did not result in sensitization but proved to be hypoallergenic.
The substance showed local antihistaminic effects.
Source: BASF AG Ludwigshafen
Test substance: sodium propionate
(163) (88)

Type: other: Human data
Remark: eye/mucosal irritation/human

10% solution, pH 7,2, not irritant, slight transient stinging to the conjunctiva and nasal mucosa.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(88)

Type: other: Human data
Remark: skin irritation/human

20% solution, pH 7–8,5 not irritant.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(88)

Type: other: Human data
Remark: skin irritation/human
Sodium propionate powder not irritating in clinical use.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(164)

Type: other: Human data
Remark: case study

Daily doses of 6g in an adult showed no toxic effect. A sligt alkalinisation of urine occured.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(78) (88)

Type: other: Human data
Remark: clinical exp./ sensitization

chronic topical use of 10% sodium propionate solution in clinical trials did not result in sensitization but proved to be hypoallergenic.
The substance showed local antihistaminic effects.
Source: BASF AG Ludwigshafen
Test substance: sodium propionate
(163) (88)

Type: other: Human data
Remark: eye/mucosal irritation/human

10% solution, pH 7,2, not irritant, slight transient stinging to the conjunctiva and nasal mucosa.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(88)

Type: other: Human data
Remark: skin irritation/human

20% solution, pH 7-8,5 not irritant.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(88)

Type: other: Human data
Remark: skin irritation/human
Sodium propionate powder not irritating in clinical use.
Source: BASF AG Ludwigshafen
Test substance: Sodium propionate
(60)

Type: other: Quantitative structure-activity relationships (QSARs) for skin corrosivity of organic acids, bases and phenols: Principal components and neural network analysis of extended datasets
Source: BASF AG Ludwigshafen
(165)

Type: other: Review
Remark: Zusammenfassende Darstellungen
Source: BASF AG Ludwigshafen
(166) (167) (168) (169) (170) (171) (172) (52) (164) (173) (106) (127) (174) (175) (176) (177) (61)

Type: other: Review
Remark: Zusammenfassende Darstellungen
Source: BASF AG Ludwigshafen
(166) (58) (109) (169) (178) (179) (180) (52) (60) (173) (106) (127) (174) (175) (176) (177) (61)

Type: other: Review
Source: BASF AG Ludwigshafen
(181)

Type: other: Review
Source: BASF AG Ludwigshafen
(182)

Type: other: Review
Source: BASF AG Ludwigshafen
(183)

Type: other: Skin corrosivity potential of fatty acids: In vitro rat and human skin testing and QSAR studies
Source: BASF AG Ludwigshafen
(184)

Type: other: The study of induced antimutagenesis of propionic acid bacteria
Source: BASF AG Ludwigshafen
(185)

Type: other: The use of in vitro cytotoxicity measurements in QSAR methods for the prediction of the skin corrosivity potential of acids
Source: BASF AG Ludwigshafen
(186)

Type:
Remark: Narcotic effects; Rat
ED50 of 1,0m solution of sodium propionate 2800mg/kg i.p. with duration of narcosis 4-30min.
0,5m solution was not effective, ED50 i.v. about 1/10 of dose, s.c. weaker action, oral no narcotic effect, no influence of
Source: BASF AG Ludwigshafen
(77)

Type:
Remark: Narcotic effects; Rat
ED50 of 1,0m solution of sodium propionate 2800mg/kg i.p. with duration of narcosis 4-30min.
0,5m solution was not effective, ED50 i.v. about 1/10 of dose, s.c. weaker action, oral no narcotic effect, no influence of
Source: BASF AG Ludwigshafen

(78)

5.11 Experience with Human Exposure

Remark: Akute Einwirkungen von Propionsaeure fuehrte bei Arbeitern zu leichten bis mittleren hautreizungen, leichten Augenreizungen und in einem Fall zu Husten und asthmatischen Beschwerden. 8 h-Konzentrationen < 0.25 ppm mit Spitzen bis zu 2.1 ppm fuehrten zu keinen Reizungen.
Source: BASF AG Ludwigshafen

(187)

Remark: 15 %-ige Loesungen von Na-Propionat rufen an der menschlichen Konjunktiva nur eine voruebergehende Roetung mit Brennen hervor, 5 %-ige Loesungen, speziell im ph-Bereich von 7-8.5, erzeugen keinerlei Reizsymptome.
Source: BASF AG Ludwigshafen

(188)

Remark: Bei einstuendiger Einwirkung von Propionsaeure nach 40 Minuten Hauterythem mit Schmerzen und geringfuegiger Nekrose nach 1 Stunde.
Source: BASF AG Ludwigshafen

(189)

Remark: Orale Gabe von 6 g Na-Propionat fuehrte zur Alkalisierung des Harns. Nebenwirkungen wurden keine beobachtet.
Source: BASF AG Ludwigshafen

(190)

Remark: Die Behandlung mit L-Carnitin fuehrte zur verstaerkten Bildung und Ausscheidung von Propionylcarnitin bei drei Patienten mit Propionsaeure-Azidaemie.
Source: BASF AG Ludwigshafen

(191)

Remark: Fallbericht ueber zwei schwangere Frauen, eine davon mit leichter Propionsaeure-Azidaemie, die unter eiweissreduzierter Diaet und Carnitingabe gesunde Kinder und ohne metabolische Dekompensation zur Welt brachten.
Source: BASF AG Ludwigshafen

(192)

Remark: Erhoehte SCEs in kultivierten Humanlymphozyten bei 2.5 mM.
Source: BASF AG Ludwigshafen

(193)

Remark: 15 %-ige Loesungen von Na-Propionat rufen an der menschlichen Konjunktiva nur eine voruebergehende Roetung mit Brennen hervor, 5 %-ige Loesungen, speziell im ph-Bereich von 7-8.5, erzeugen keinerlei Reizsymptome.
Source: BASF AG Ludwigshafen
(188)

Remark: Bei einstuendiger Einwirkung von Propionsaeure nach 40 Minuten Hauterythem mit Schmerzen und geringfuegiger Nekrose nach 1 Stunde.
Source: BASF AG Ludwigshafen
(189)

Remark: Orale Gabe von 6 g Na-Propionat fuehrte zur Alkalisierung des Harns. Nebenwirkungen wurden keine beobachtet.
Source: BASF AG Ludwigshafen
(190)

Remark: Die Behandlung mit L-Carnitin fuehrte zur verstaerkten Bildung und Ausscheidung von Propionylcarnitin bei drei Patienten mit Propionsaeure-Azidaemie.
Source: BASF AG Ludwigshafen
(191)

Remark: Fallbericht ueber zwei schwangere Frauen, eine davon mit leichter Propionsaeure-Azidaemie, die unter eiweissreduzierter Diaet und Carnitingabe gesunde Kinder und ohne metabolische Dekompensation zur Welt brachten.
Source: BASF AG Ludwigshafen
(192)

Remark: Erhoehte SCEs in kultivierten Humanlymphozyten bei 2.5 mM.
Source: BASF AG Ludwigshafen
(193)

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7.1 Risk Assessment

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Table I. Metal Salts of C2 and C3 Carboxylates and Their Dissociation Products: Existing Data for Substance Information and Physicochemical Properties

Data Element		Acetic Acid	Cobaltous Acetate	Propionic Acid	Propionic Acid, Cobalt (II) Salt	Cobalt (as Cobaltous Chloride)
1.01	**Substance Information**					
A	**CAS No.**	64-19-7	71-48-7	79-09-4	1560-69-6	7646-79-9
F	**Molecular Formula**	$C_2H_4O_2$	$C_4H_6O_4Co$	$C_3H_6O_2$	$C_6H_{10}O_4Co$	$CoCl_2$
F	**Molecular Weight**	60.05	177.0	74.08	205.1	129.84
2	**Physical-chemical Data**					
2.1	**Melting Point (°C)**	16.7 [1]	--* [3a]	-21.5 [4]	--* [3d]	735 [4]
2.2	**Boiling Point (°C)**	118.1 [1]	--* [3b]	141.1 [4]	--* [3e]	1049 [4]
2.4	**Vapor Pressure**	11.4 mm Hg @20°C [1]		1 kPa @35.1°C [6]		
2.5	**Partition Coefficient (log K_{ow})**	-0.17 [1]		0.33 [6]		
2.6.1	**Water Solubility**	50 g/L @20°C [1]	2.9 mg/L @20°C [3c]	Miscible [4]	43.4 @20°C [3f]	Soluble [4]
	Dissociation Constant, pKa	4.76 @25°C [2]	7.75 and 4.91 @20°C [5]	4.87 [7]	7.58 and 4.85 @20°C [5]	Not applicable

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Table II Metal Salts of C2 and C3 Carboxylates and Their Dissociation Products: Existing Data for Environmental Fate SIDS Elements

Data Element		Acetic Acid	Cobaltous Acetate	Propionic Acid	Propionic Acid, Calcium Salt	Propionic Acid, Cobalt (II) Salt	Cobalt (as Cobaltous Chloride)
3	**Environmental Fate & Pathways**						
3.1A	**Photodegradation**	5.1×10^{-13} cm^3/molecule· sec; 50% degradation after 21 days; [1] (calculated value)					
3.1B	**Stability in Water**						Stable
3.3.	**Transport and Distribution (Fugacity)**	Level I: 26.9% (air); 73.1% (water); 0.044% (soil) (calculated)					
3.4	**Aerobic Biodegradation**	Readily biodegradable; 99% after 7 days under anaerobic conditions using activated sludge; [2]		Readily biodegradable; 95% in 10 days (activated sludge) [3]	Readily biodegradable; 100% in 7 days OECD 302B (activated sludge) [4]		Not applicable
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Table III. Metal Salts of C2 and C3 Carboxylates and Their Dissociation Products: Existing Data for Ecotoxicity

Data Element		Acetic Acid	Cobaltous Acetate	Propionic Acid	Propionic Acid, Cobalt (II) Salt	Cobalt (as Cobaltous Chloride)
4	**Ecotoxicity**					
4.1	**Acute Toxicity to Fish** 96-h LC50 EC50 (mg/L except for $CoCl_2$ which is expressed as mg Co/L)	75 (bluegill);[1] 251 (mosquito fish) [2]		67.1 (rainbow trout) 85.3 (bluegill) [5]		1.41 (rainbow trout)[9], >5 (fathead minnow)[10], 333 (carp) [11]
4.2	**Acute Toxicity to Invertebrates** 48-h EC50 (mg/L except for $CoCl_2$ which is expressed as mg Co/L)	65 (*Daphnia magna*) (un-neutralized) [3]		22.7 mg/L (*Daphnia magna*) [5]		1.11 and 1.62 [12]; 1.49, [13]; 1.52[14]; 5.5 [15]. (*Daphnia magna*)
4.3	**Toxicity to Aquatic Plants (e.g., algae)** EC50 (mg/L except for $CoCl_2$ which is expressed as mg Co/L)	8-day growth inhibition; toxicity threshold = 4,000 *Scenedesmus quadricauda*, [4]		72-h EC50 = 45.8 (*Scenedesmus subspicatus*) [6]		96-h EC50 = 0.522 (*Chlorella vulgaris*) [16]

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Table IV. Metal Salts of C2 and C3 Carboxylates and Their Dissociation Products: Existing Data for Mammalian Toxicity - SIDS Elements

Data Element		Acetic Acid	Cobaltous Acetate	Propionic Acid	Propionic Acid, Cobalt (II) Salt	Cobalt (as Cobaltous Chloride)
5	**Mammalian Toxicity**					
5.1	**Toxicokinetics, metabolism, distribution**			Is a normal intermediary metabolite in animals and humans		The soluble form, cobalt chloride, is absorbed 13-34% in the gut of rats. Following oral exposure, cobalt is eliminated primarily in feces and secondarily in urine. [22].
5.2A	**Acute Oral Toxicity LD50** (mg/kg bw except for $CoCl_2$ which is expressed as mg Co/kg bw)	4,960 (mouse) [1]	503 (rat) (168 when expressed as mg Co/kg bw)[9]	2,600 – 4,290 (rat) [14], [15]; [16]		42.4 to 190 mg Co/kg bw (rat) ; [22]; 89.3 (mouse) mg Co/kg bw; [22]
5.5	**Repeated Dose Toxicity**	Induced hyperplasia in rats @ 60 mg/kg bw (oral; 3 times/wk for 8 mon.) [2];. Increased spleen and kidney weights, kidney damage @ 23-31 mg/kg/ bw (inhalation; continuous 3 – 35 days); [3].		90-d NOAEL (rat) = 6,200 ppm in feed (517 mg/kg bw/d), [17]; 1-yr NOAEL (rat)= 20,000 ppm in diet (1,320 mg/kg bw/d) for sodium salt, [18]		5-mon LOAEL (liver, kidney) = 10 mg Co/kg/day ([23]; [24]). LOAEL (rat, cardiovascular) = 12.4 mg Co/kg/day for 3 wk; [25]. LOAEL (hematological) = 0.5 mg Co/kg/day and above for 3 wk to 2 mon. [22].
5.6	**Genetic Toxicity *in vitro***	Negative [4]; Negative [5]; Negative [6]. Cytotoxic due to low pH, but not clastogenic; [7].	Very weak to weak positive in *Salmonella* assay; [10]. Enhanced transformation of adenovirus I hamster embryo cells; [11].	Negative in Ames *Salmonella* Assay, [19]		Cobalt compounds with a valence state of II, the form of cobalt released by dissociation of cobalt salts, are reported to be generally non-mutagenic in bacterial assays, but increased frequency of genetic conversions have been reported in yeast.

Data Element		Acetic Acid	Cobaltous Acetate	Propionic Acid	Propionic Acid, Cobalt (II) Salt	Cobalt (as Cobaltous Chloride)
5.7	**Genetic Toxicity *in vivo***		Negative in mouse micronucleus test; [10]	Negative in hamster micronucleus assay, [20]		Cobalt compounds, including salts, are observed to be genotoxic or mutagenic in mammalian systems. Cobalt compounds, including cobalt salts, are reported to be clastogenic in mammalian cells.
5.9A	**Reproductive Toxicity / Fertility**					Rat NOAEL = 5 mg Co kg bw/day. Nation et al., 1983. Testicular degeneration and atrophy have been reported in rats exposed to 13.2 to 58.9 mg Co/kg/day for 2-3 months in the diet or drinking water or in mice exposed to 43.4 mg Co/kg/day in drinking water for 13 weeks [22].
5.9B	**Developmental Toxicity / Teratology (offspring)**	No effects on nidation or on maternal or fetal survival in mice, rats and rabbits at oral doses up to 1600 mg/kg bw/day; [8]	Not teratogenic to chicken embryos up to lethal level; [12]. Tetrahydrate at 5 mg/kg did not induce embryocidal or teratogenic effects in golden hamsters; [13].			Rat fetus LOAEL = 5.4 mg Co/kg/day (stunted pup growth). No teratogenic effects. Rat NOAEL = 24.8 mg Co/kg/day. Mouse NOAEL = 81.7 mg Co/kg/day. [22]
6.0	**Other Mammalian Toxicity Studies**			Dysplasia, hyperplasia, and precancerous lesions in the forestomachs of rats fed 4% (2640		The U.S. National Toxicology Program does not recognize cobalt as a human carcinogen, but IARC has classified cobalt

Data Element		Acetic Acid	Cobaltous Acetate	Propionic Acid	Propionic Acid, Cobalt (II) Salt	Cobalt (as Cobaltous Chloride)
				mg/kg/d) in diet over lifetime [21].		and cobalt compounds as possibly carcinogenic to humans (Class 2B) based on sufficient evidence that cobalt metal powder and cobaltous oxide are carcinogenic in animals.

References: 1) Woodward et al., 1941; 2) Alexandrov et al., 1989; 3) Savina and Anisimov, 1987; 4) McMahon et al., 1979; 5) Zeigler et al., 1992; 6) BIBRA, 1993; 7) Morita et al., 1990; 8) FDRF, 1974; 9) Speijer et al., 1982; 10) Turoczi et al., 1987; 11) Castro et al., 1979; 12) Verrett et al., 1980; 13) Ferm and Carpenter, 1968; 14) WHO 1974; 15) BASF, 1969; 16) Symth et al. 1962; 17) BASF, 1971; 18) Imai et al., 1981; 19) NTP, 1988; 20) Basler et al., 1987; 21) Altman and Grunow, 1985; 22) ATSDR, 2001; 23) Murdock 1959, .24) Holly 1955; 25) (Morvai et al. 1993.

1. General Information

ID 71-48-7
Date April 24, 2005

201-16106A

Note: Appendix A1 is the attached HPV Submission for the Acetic Acids and Salts Panel (June 28 2001).

1.0 SUBSTANCE INFORMATION

Generic Name	:	Cobalt acetate
Chemical Name	:	Cobaltous acetate
CAS Registry No.	:	71-48-7
Component CAS Nos.	:	
EINECS No.	:	200-755-8
Structural Formula	:	$Co(C_2H_3O_2)_2$
Molecular Weight	:	177.03
Synonyms and Tradenames	:	Acetic acid, cobalt(2+) salt Cobalt diacetate
References	:	

2.1 MELTING POINT

Type	:	
Guideline/method	:	OECD 102
Value	:	None °C
Decomposition	:	>120°C
Sublimation	:	
Year	:	2003
GLP	:	Yes
Test substance	:	Cobalt acetate
Method	:	OECD 102 using differential scanning calorimetry and capillary tester
Method detail	:	Test item was heated from 25°C to 400°C at a rate of 20 K/min in a calorimeter and absorption and release of heat was monitored. In the final study the actual melting point range with a temperature rise to 5 K/min in the range of 180°C to 260°C. The latter test was replicated and the weight and appearance of the sample was determined before and after to test. A third study was conducted by heating sample at 20 K/min starting at 25°C and ranging to 400°C with a capillary tube packed tightly and heated at.
Result	:	The test item does not melt under the conditions of the test and degradation occurs at 210°C and above.
Remark	:	**Supporting data for dissociation products:** **Acid:** M.P. reported as 16.7°C (see Acetic Acid and Salts Category Robust Summaries)
Reliability	:	[1] Reliable without restriction
Reference	:	Tognucci, A. 2003. Determination of the Melting Point /Melting Point Range of Cobalt Acetate. RCC, Ltd. Environmental Chemistry & and Pharmanalytics, CH-4452 Intingen/Switzerland, RCC Study #849047

2.2 BOILING POINT

Type	:	
Guideline/method	:	OECD 103
Value	:	Not determined under conditions of test
Decomposition	:	
Year	:	2003
GLP	:	Yes
Test substance	:	Cobalt acetate
Method	:	Differential scanning calorimeter (DSC)and thermal analysis using capillary tester
Method detail	:	In the preliminary phase DSC was used to compare sample held in a an aluminum dish to an empty (reference) dish and the difference in heat flow between the two containers was measured as the test item was heated from 25°C to 400°C at a rate of 20 K/min. Definitive boiling point was evaluated using the capillary method filling a boiling tube with sample and boiling capillary tubes added. Evolution of bubbles in the capillary tubes was used as a visual indiactor of boiloing point when sample was heated from25°C to 400°C at a rate of 20 K/min .
Result	:	Boiling point range could not bedetermined under the conditions of the study
Remark	:	**Supporting data for dissociati products:** **Acid:** B.P. reproted as 118.1°C (see Acetic Acid and Salts Category Robust Summaries)
Reliability	:	[1] Reliable without restrictions
Reference	:	Tognucci, A. 2003. Determination of the Boiling Point /Boiling Point Range of Cobalt Acetate. RCC, Ltd. Environmental Chemistry & and Pharmanalytics, CH-4452 Intingen/Switzerland, RCC Study #849048

2.3 DENSITY

Type	:	
Guideline/method	:	
Value	:	at °C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference		

2.4 VAPOR PRESSURE

Type	:	
Guideline/method	:	
Value	:	hPa at °C
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acids:** 15.2 hPa (11.4 mm Hg) @ 20°C (Appendix A1)
Reliability	:	
Reference	:	

2.5 PARTITION COEFFICIENT

Type	:	
Guideline/method	:	
Partition coefficient	:	
Log Pow	:	at °C
pH value	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Acetic Acid (CAS 64-19-7) Log Kow = -0.17 (see Appendix A1)
Reliability	:	
Reference	:	

2.6.1 SOLUBILITY IN WATER

Type	:	
Guideline/method	:	OECD 105
Value	:	2.9 mg/L cobalt acetate (± 0.4 mg/L) at 20°C
pH value	:	7.10 to 7.51

concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
PKa	:	7.75 and 4.91 at 20°C
Description	:	
Stable	:	
Deg. product	:	Acetate and Co^{+2}
Year	:	2003
GLP	:	Yes
Test substance	:	Cobalt acetate
Deg. products CAS#	:	CAS #64-19-7, CAS #
Method		Simplified flask method and column elution method
Method detail	:	In a preliminary test cobalt propionate was evaluated using a simplified flask method with an abbreviated equilibration time to determine if the test material had a solubility above or below 10 mg/L. This was established (<10 mg/L) and the definitive test used the column elution method. Glass beads (5.98 g) were weighed and transferred into a round bottom flask (25 ml) and test material (0.123 g) was weighed and added to the flask. The mixture was thoroughly shaken. The loaded beads were were added to elution column which was filled with water. Elution of Co propionate was performed using a circulation pump . Flow rate was adjusted and the column allowed to run until five consecutive samples (1 hr apart) did not differ by more than 30%. A second part of the experiment was conducted at half of the initial flow rate to confirm saturation. Analysis was conducted using atomic absorption spectrophotometry
Result	:	2.9 mg/L cobalt acetate (± 0.4 mg/L) which corresponds to a water solubility of the test item of 8.6 mg/L.
Remark	:	**Supporting data for dissociation products:** **Acid:** Acetic acid (CAS 64-19-7) Solubility is50 g/L @20°C (App. 1)
Reliability	:	[1] Reliable without restrictions
Reference	:	Tognucci, A. 2003. Determination of Water Solubility of Cobalt Acetate. RCC, Ltd. Environmental Chemistry & and Pharmanalytics, CH-4452 Intingen/Switzerland, RCC Study #849050

2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	°C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.1.1 PHOTODEGRADATION

Type		
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) :
		epsilon (max) :
		epsilon (295) :
Conc. of substance	:	at °C
DIRECT PHOTOLYSIS		
Halflife (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Acetic acid (94-19-7) calculated value of ~ 50% after 21 days. **Metal:** NA
Reliability	:	
Reference	:	

3.1.2 DISSOCIATION

Type	:	Dissociation constant determination
Guideline/method	:	OECD 112
pKb	:	7.75 and 4.91 at 20°C
Year	:	2002
GLP	:	Yes
Test substance	:	Cobalt (II) acetate (399973-10G), lot number 04119D0, received from Aldrich Chemical Company. Light purple powder, purity of 99.995+%.
Approximate water solubility	:	14,000 mg/L, as determined visually in preliminary study
Method	:	OECD Guideline 112, Dissociation Constants in Water
Method detail	:	Three replicate samples of cobalt acetate were prepared at a nominal concentration of 0.01 moles/L by dissolving 0.1770 grams of the test substance in 100 mL degassed water (ASTM Type II). Each sample was titrated against 0.1 N hydrochloric acid while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the equivalence point and the titration was carried past the equivalence point. Values of pK were calculated for a minimum of 10 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.
Result	:	Mean (N = 3) pKb values were 7.75 (SD = 0.0610) and 4.91 (SD = 0.0389) at 20°C
Remark	:	The results indicate that dissociation of the test substance will occur at

environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).

Reliability : [1] Reliable without restriction.
Reference : Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of cobalt acetate, Wildlife International, Ltd. Study No. 534C-112, conducted for the Metals Carboxylate Coalition.

3.2.1 MONITORING DATA

Type of measurement :
Media :
Concentration :
Substance measured :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.3.1 TRANSPORT (FUGACITY)

Type : Level III Fugacity Model
Media :
Air : % (Fugacity Model Level III)
Water : % (Fugacity Model Level III)
Soil : % (Fugacity Model Level III)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Year :
Test substance : Co acetate
Method : EPIWIN 3.11
Method detail :
Result :

	Mass Amount (percent)	Half-life (hr)	Emissions (kg/hr)
Air	0.000801	3.04×10^3	1000
Water	45.2	360	1000
Soil	54.7	360	1000
Sediment	0.0755	1.44×10^3	0

Persistance time 421 hr

Remark : **Supporting data for dissociation products:**
Acid: Level I fugacity modeling with acetic acid (CAS 64-19-7) provided estimated partitioning to respective compartments of: 26.9% (air), 73.1% (water), 0.044% (Soil), 97.2×10^{-4}% (sediment), 3.04×10^{-5}% (suspended sediment) and 2.47×10^{-6}% (fish) (see Appendix A1).
Metal: NA
Reliability : [2]
Reference : EPIWIN 3.11

3.5 BIODEGRADATION

Type :
Guideline/method :
Inoculum :
Concentration : related to
related to

Contact time	:	
Degradation	:	(±) % after day(s)
Result	:	
Kinetic of test subst.	:	% (specify time and % degradation) % % % %
Control substance	:	
Kinetic	:	% %
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Acetic acid (94-19-7). Readily biodegradable. 99% reduction after 7 days in sewage treatment medium (see Appendix A1). **Metal:** NA
Reliability	:	
Reference	:	

3.7 BIOCONCENTRATION

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	at °C
Concentration	:	
BCF	:	
Elimination	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

4.1 ACUTE TOXICITY TO FISH

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
LC0	:	
LC50	:	
LC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Acetic acid (CAS 64-19-7) The 96-h LC50 is reported as 75.0 mg/L for *Lepomis macrochirus* and 251 mg/L for *Gambusia affinis* Acetic acid **Metal:** The reported 96-h LC50 is 333 mg Co/L for *Cyprinus carpio* and 1,406 mg Co/L for *Onchorynchus mykiss* (ECOTOX data base).).
Reliability	:	
Reference	:	

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
EC0	:	
EC50	:	
EC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The 24 hour EC50s for *Daphnia* exposed to acetic acid (CAS 64-19-7) under static conditions ranged from 47.0 mg/L to 95.0 mg/L and the 48 hour EC50 was reported as 65.0 mg/L. When water was neutralized prior to introducing the organisms the EC50 was 6,000 mg/L. (see Appendix A1).

Metal: The reported 48-h EC50 values for *Daphnia magna* range from 1.11 to 5.6 mg Co/L (ECOTOX data base).

Reliability :
Reference :

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type :
Guideline/method :
Species :
Endpoint :
Exposure period :
NOEC :
LOEC :
EC0 :
EC10 :
EC50 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :

Supporting data for dissociation products:
Acid: The toxicity threshold for *Scenedesmus quadracauda* is reported as 4,000 mg/L after an 8-d exposure. Growth inhibition was the most sensitive measure of effect. (see Appendix A1).
Metal: The reported 96-h EC50 for *Chorella vulgaris* is 0.522 mg Co/L (ECOTOX data base).

Reliability :
Reference :

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:	
Type	:	
Guideline/method	:	
Species	:	
Number of animals	:	
Males	:	
Females	:	
Doses	:	
Males	:	
Females	:	
Vehicle	:	
Route of administration	:	
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1st: 2nd: 3rd:
Toxic behavior	:	
Deg. product	:	
Deg. products CAS#	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** **Metal:** Absorption of cobalt in the digestive tract is influenced by the chemical form of the metal. The soluble form, cobalt chloride, is absorbed 13-34% in the gut of rats, but absorption in the gut may be increased in iron deficient individuals. Following oral exposure, cobalt is eliminated primarily in feces and secondarily in urine. For the more soluble forms of cobalt, e.g., cobalt chloride, 70 – 80% of the administered dose is eliminated in the feces. For absorbed cobalt, elimination is rapid primarily in the urine (Barceloux, D.G. (1999) Cobalt. Clin. Tox. 37(2):201-206). Elimination is biphasic or triphasic. The terminal phase involves a very small residual level of cobalt and has a half-life in years (ATSDR Sept 2001 Draft Toxicological Profile for Cobalt, U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry) (Subsequently listed as ATSDR Sept 2001 Draft).
Reliability	:	
Reference	:	

5.1.1 ACUTE ORAL TOXICITY

Type	:	Single dose
Guideline/Method	:	
Species	:	Rat
Strain	:	Wistar
Sex	:	Both male and female

Number of animals	:	5 per sex
Vehicle	:	Compound was administered either in distilled water or as a suspension of an Ultra-Turrax in a 1% carboxymethylcellulose solution.
Doses	:	250, 375, 560, 840, and 1260 mg/kg
LD50	:	503 mg/kg based on the weight of anhydrous compound 708 mg/kg based on the weight of the tetrahydrate compound 168 mg/kg based on the weight of cobalt(II) ion
Year	:	1981
GLP	:	
Test substance	:	Cobalt(II) acetate tetrahydrate; purity = 99%
Method	:	Gastric intubation
Method detail	:	Signs of reactions and deaths were recorded for 10 days, and the rectal temperature was measured in all surviving rats 1.5, 24, and 48 hours after administration of the compound.
Result	:	Respiratory disturbances were apparent before death. Body temperature was also reduced after administration.
Remark	:	Eight different cobalt(II) compounds were included in this study including cobalt chloride, cobalt bromide, cobalt fluoride and cobalt sulfate. Calculated on the basis of the cobalt(II) ion, the acute oral toxicities of the cobalt compounds tested were similar with LD50 values ranging from 91 to 168 mg Co/kg. Except for the bromide and fluoride compounds, which showed a somewhat higher acute toxicity, the contribution of the cation to the toxicity of the compound was negligible compared with that of the cobalt anion. The mouse LD50 for cobalt acetate is reported as 28 mg/kg when administered intravenously. (Venugopal and Luckey1978 cited in the Hazardous Substance Databank (HSDB)) **Supporting data for dissociation products:** **Acid:** The mouse LD50 for acetic acid (CAS 64-19-7) is reported as 4960 mg/kg b.w. (see Appendix A1) **Metal:** Acute oral toxicity values of the cobalt portion of the cobalt salts in this category are compared to simple cobalt salts such as cobalt chloride and cobalt sulfate. Reported LD50s of cobalt chloride to rats range from 42.4 to 190 mg $CoCl_2$/kg bw (equivalent to 19.8 to 85.5 mg Co/mg bw) (ATSDR Sept 2001 Draft). Toxicity of cobalt sulfate reported to be similar to the chloride with the oral LD50s for rats ranging from 123 to 161 mg/kg bw (equivalent to 46.7 to 61.2 mg Co/kg b.w. (ATSDR Sept 2001 Draft). For the mouse, LD50 values were reported as 89.3 and 123 mg/kg for cobalt chloride and the cobalt sulfate, respectively, which are equivalent to 40.2 and 46.7 mg Co/mg b.w. when expressed as metal (ATSDR Sept 2001 Draft).
Reliability	:	(2) Reliable with restrictions.
Reference	:	Speijers, G.J.A., E.I. Krajnc, J.M. Berkvens, and M.J. van Logten. 1982. Acute oral toxicity of inorganic cobalt compounds in rats. Food Chem. Toxicol., 20:311-314.

5.1.2 ACUTE INHALATION TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	

Doses	:	
Exposure time	:	
LC50	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Acetic acid (94-19-7) has a reported inhalation LC50 of 11.0 mg/L in rats exposed for four hours. In mice the 1.0-h LC50 was 5,620 mg/L (see Appendix A1). **Metal:** The acute LC50 for a 30-minute inhalation exposure in rats was 165 mg cobalt/m3 as mixed cobalt oxides. (ASTDR, 1992, Toxicological Profile for Cobalt). In a 1 hour exposure to a dust aerosol of cobalt powder, the LC50 for rats was > 10 mg/L (IUCLID, 2000).
Reliability	:	
Reference	:	

5.1.3 ACUTE DERMAL TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
LD50	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The dermal LD50 for acetic acid (94-19-7) to the rabbit is reported as 1060 mg/kg b.w.(see Appendix A1). **Metal:** Increased proliferation of lymphatic cells was seen in mice and guinea pigs dermally exposed to cobalt chloride, with LOAEL values ranging from 9.6 to 14.7 mg Co/kg/day. (ATSDR Sept 2001 Draft).
Reliability	:	
Reference	:	

5.2.1 SKIN IRRITATION

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	

Vehicle	:	
Classification	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Metal:** Cobalt is reported to be irritating to the skin (IUCLID, 2000).
Reliability	:	
Reference	:	

5.2.2 EYE IRRITATION

Type	:
Guideline/method	:
Species	:
Strain	:
Sex	:
Concentration	:
Dose	:
Exposure time	:
Number of animals	:
Vehicle	:
Classification	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

5.4 REPEATED DOSE TOXICITY

Type	:
Guideline/method	:
Species	:
Strain	:
Sex	:
Number of animals	:
Route of admin.	:
Exposure period	:
Frequency of treatment	:
Post exposure period	:
Doses	:
Control group	:
NOAEL	:
LOAEL	:
Other	:
Year	:
GLP	:
Test substance	:
Method	:

Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Rats dosed with 0.5 ml of a 3.0% solution of acetic acid (CAS 64-19-7) 3 times weekly for 8 months did not induce tumors although hyperplasia in the esophagus and forestomach was observed in exposed rats. In a parallel treatment group treatement with a known carcinogen NSEE did resulty in tumors. The esophagus and forestomach showed pre-neoplastic lesions, benign tumors, carcinomas, and squamous cell cancer. Treatment with acetic acid and NSEE combined resulted in increased levels of benign and malignant tumors, carcinomas in the esophagus. (see Appendix A1). **Metal**: Repeated oral dosing of rats with cobalt chloride at levels ranging from 0.5 to 30.2 mg Co/kg/day (as cobalt chloride) for periods ranging from 12-16 days up to 7 months resulted in the following observations associated with LOAELs: reduced weight gain, increases in some organ weights (heart, liver and lungs); increased hematocrit, hemoglobin, and RBCs; renal tubular necrosis; and various changes on cardiac physiology (left ventricular hypertrophy, impaired ventricular function, and degeneration of myofibrils) (ATSDR Sept 2001 Draft). Cardiac effects were observed in rats at LOAEL's ranging from 8.4 to 12.4 mg Co/kg/day, for cobalt sulfate or cobalt chloride, with exposure periods of 3 weeks to 6 months (ATSDR Sept 2001 Draft).
Reliability	:	
Reference	:	

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Mutagenicity
Guideline/method	:	*Salmonella*/Microsomal Mutagenicity Assay
System of testing	:	Bacteria
Species	:	*Salmonella*
Strains	:	5 (not specified)
Test concentrations	:	0.03 to 10.0 mg/plate
Cytotoxic concentr.	:	Not specified
Metabolic activation	:	No
Year	:	1987
GLP	:	Not specified
Test substance	:	Cobalt acetate
Method	:	
Method detail	:	
Result	:	Very weak to weak mutagenicity was detected at 10.0 mg/plate in three of five tester strains, but none was observed in any strains at lower levels (3.3, 0.33, and 0.3 mg/plate).
Remark	:	**Supporting data for dissociation products:** **Acid:** Acetic acid (CAS 94-19-7) is negative in a bacterial reverse mutation assay with and without activation using strains TA 98, TA 100, TA1535 and TA1538. The same results were observed in a study using TA 98, TA 100, TA1535 and TA 97 or TA1538. This study was negative with and without activation. In a third study acetic acid and as sodium and zinc salts showed no evidence of mutagenicity using *Salmonella typhimurium* with and without activation (see Appendix A1). In a non-bacterial *in vitro* study with Chinese hamster ovary K1 cells, acetic acid was not clastogenic at concentrations close to those showing cytotoxicity.(see Appendix A1). **Metal:** Cobalt compounds with a valence state of II, the form of cobalt released by dissociation of cobalt salts, are reported to be non-mutagenic in bacterial assays (ATSDR Sept 2001 Draft), but cobalt compounds with a valence state of III were weakly mutagenic.

Reliability	:	(2) Reliable with restrictions. Basic information available in an abstract only.
Reference	:	Turoczi, L.J., M. Bauzon, and L. Kocur. 1987. A genotoxic analysis of cobaltous acetate using the Salmonella mutagenicity assay and the mouse micronucleus test. Abstract 284. Environ, Mutagen. Vol 9, Suppl 8, pg 109.
Type	:	Mutagenicity (cell transformation, viral enhanced)
Guideline/method	:	
System of testing	:	Adenovirus transformation in hamster embryo cells
Species	:	Syrian hamster (host); Simian adenovirus SA7 (virus)
Strain	:	
Test concentrations	:	Not specified
Cytotoxic concentr.	:	Not specified
Metabolic activation	:	
Year	:	1979
GLP	:	Not specified
Test substance	:	Cobalt acetate
Method	:	
Method detail	:	
Result	:	Cobalt acetate at a concentration of 0.2 mM enhanced transformation of the SA7 adenovirus by a factor or 7.2-fold suggesting that it is potentially mutagenic.
Remark	:	
Reliability	:	(2) Reliable with restrictions.
Reference	:	Castro, B.C., J. Myers, and J.A. DiPaolo. 1979. Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. Cancer Res. 39: 193-198.

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	
Guideline/method	:	Mouse micronucleus test
Species	:	Mouse
Strain	:	Not specified
Sex	:	Not specified
Route of admin.	:	I.P. injection
Exposure period	:	
Dose	:	33 mg/kg
Year	:	1987
GLP	:	Not specified
Test substance	:	Cobaltous acetate
Method	:	
Method detail	:	
Result	:	Nonmutagenic (Note slight paralysis and related difficulties were seen in mice exposed at 100 mg/kg)
Remark	:	**Supporting data for dissociation products:** **Acid:** **Metal:** Cobalt compounds, including salts, are observed to be genotoxic or mutagenic in a range of mammalian systems. For example, increased micronucleus formation was observed following i.p. injection of 12.4 and 22.3 mg Co/kg (as cobalt chloride), but not after injection of 6.19 mg Co/kg (NOEL) (ATSDR Sept 2001 Draft).
Reliability	:	(2) Reliable with restrictions. Basic information available in an abstract only.
Reference	:	Turoczi, L.J., M. Bauzon, and L. Kocur. 1987. A genotoxic analysis of cobaltous acetate using the Salmonella mutagenicity assay and the mouse micronucleus test. Abstract 284. Environ. Mutagen. Vol 9, Suppl 8, pg 109.

5.8.2 DEVELOPMENTAL TOXICITY

Type	:	Teratogenicity
Guideline/method	:	Egg injection
Species	:	Chicken
Strain	:	Single-Comb White Leghorn
Sex	:	
Route of admin.	:	Injection through yolk and air cell
Exposure period	:	Through hatching
Frequency of treatment	:	Single treatment at either preincubation (0 hr) or fourth day (96 hr)
Duration of test	:	Through hatching
Doses	:	Up to 2.5 mg/egg
Control group	:	Yes (vehicle only)
NOAEL maternal tox.	:	Not applicable
NOAEL teratogen.	:	2.5 mg/egg
Other	:	LD50 = 0.10 mg/egg for injection into air cell at 0 hr
Other	:	
Other	:	
Year	:	
GLP	:	
Test substance	:	Cobaltous acetate
Method	:	
Method detail	:	Water used as vehicle for injection
Result	:	Not found to be teratogenic to chicken embryos up to a lethal level
Remark	:	Results are consistent with those of Ferm and Carrpenter (1968) who found that cobaltous acetate tetrahydrate at a dose of 5 mg/kg did not induce embryocidal or teratogenic effects when administered alone to golden hamsters. Ferm, V.H. and S.J. Carpenter. 1968. The relationship of cadmium and zinc in experimental mammalian teratogenesis. Lab Invest. 18:429-432. **Supporting data for dissociation products:** **Acid:** In 3 developmental studies with CD1 mice, Wistar rats, and Dutch-belted rabbits result showed no effects of acetic acid (CAS 64-19-7) on nidation or on maternal or fetal survival at doses up to 1600 mg/kg b.w./day (see Appendix A1). **Metal:** In a single developmental toxicity study with cobalt chloride exposure (5.4 or 21.8 mg Co/kg/day) from gestation day 14 to lactation day 21 the LOAEL was based on stunted pup growth. However, maternal toxicity was observed in conjunction with effects on the offspring. This growth effect was considered to be a secondary or indirect effect rather than a direct effect of cobalt on the fetus. No teratogenic effects were observed. Another study in rats provided a NOAEL of 24.8 mg Co/kg/day for cobalt chloride exposure from gestation days 6-15. No effects on fetal growth or survival in mice exposed to 81.7 mg Co/kg/day as cobalt chloride during gestation days 8-12 (ATSDR Sept 2001 Draft).
Reliability	:	(2) Reliable with restrictions. Method is for screening purposes only.
Reference	:	Verrett, M.J., W.F. Scott, E.F. Reynaldo, E.K. Alterman, and C.A. Thomas. 1980. Toxicity and teratogenicity of food additive chemicals in the developing chicken embryo. Toxicol. Appl. Pharmacol. 56: 265-273.

5.8.3 TOXICITY TO REPRODUCTION

Type	:	
Guideline/method	:	
In vitro/in vivo	:	
Species	:	
Strain	:	

Sex	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatment	:	
Duration of test	:	
Doses	:	
Control group	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data:** **Acid:** **Metal:** Testicular degeneration and atrophy have been reported in rats exposed to 13.2 to 30.2 mg Co/kg/day as cobalt chloride for 2-3 months in the diet or drinking water. (ATSDR Sept 2001 Draft). Similar effects were seen in mice exposed to 23 to 43.4 mg Co/kg/day as cobalt chloride in drinking water for 10-13 weeks. In addition, reduced numbers of pregnant females and pups per litter, and reduced fertility, were observed in mice at 58.9 mg Co/kg/day. (ATSDR Sept 2001 Draft).
Reliability	:	
Reference	:	

6.0 OTHER INFORMATION

6.1 CARCINOGENICITY

The US National Toxicology Program does not recognize cobalt as a human carcinogen, but IARC has classified cobalt and cobalt compounds as possibly carcinogenic to humans (Class 2B) based on sufficient evidence that cobalt metal powder and cobaltous oxide are carcinogenic in animals (Barceloux 1999, ATSDR Sept 2001 Draft). "No studies were located regarding carcinogenic effects in animals after oral exposure to stable [non-radioactive] cobalt." (ATSDR Sept 2001 Draft).